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To Honor

FREDERICK CARL CORDES, M.D.

on the occasion of his

Sixty-seventh Birthday

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FREDERICK CARL CORDES, M.D.

ON THE OCCASION OF HIS

SIXTY-SEVENTH BIRTHDAY

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For a complete table of contents see page 2

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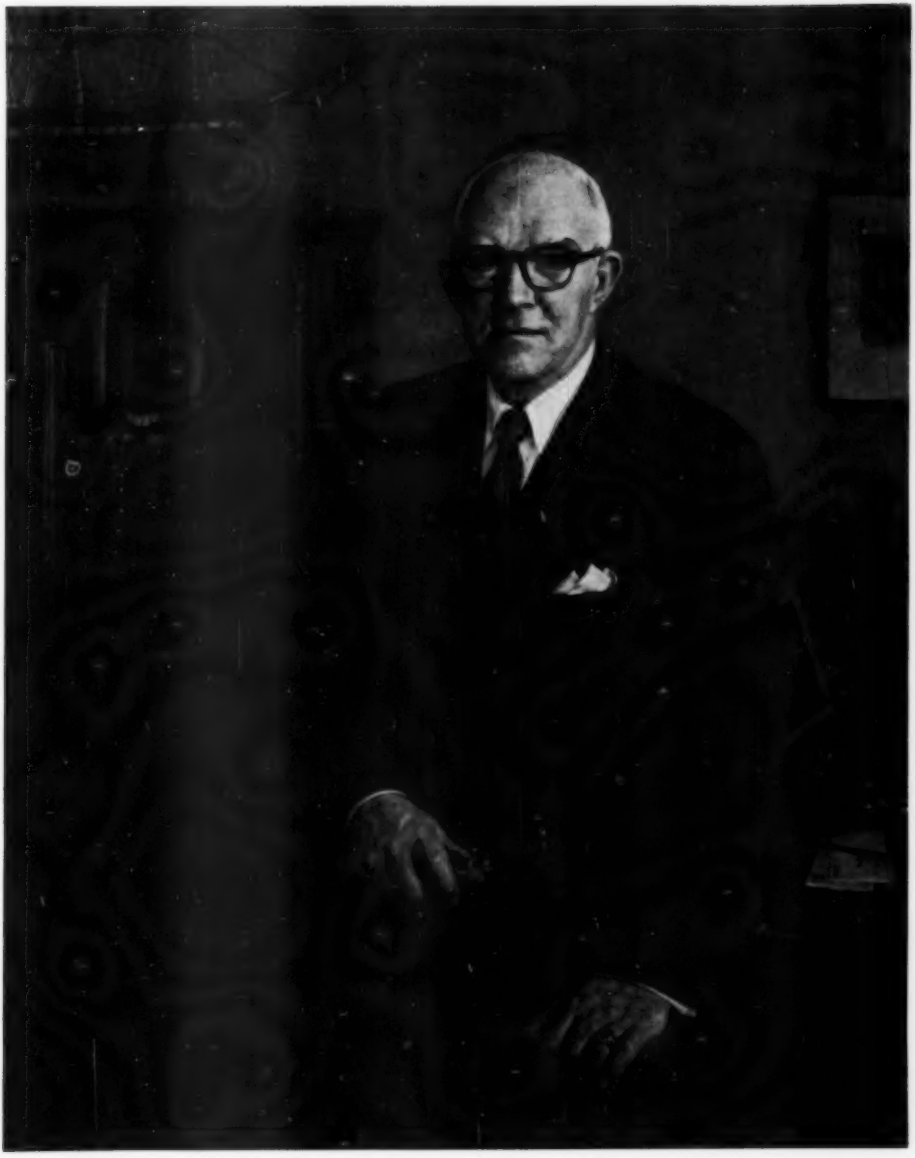

FREDERICK CARL CORDES, M.D.

The portrait of Dr. Frederick C. Cordes was presented to the University of California School of Medicine in recognition of his services and contributions to the university. The staff of the Department of Ophthalmology and his former residents commissioned the well-known San Francisco portrait artist, Mr. Arthur W. Palmer, to paint this portrait in honor of Dr. Cordes' 20 years of service as chairman of the Department of Ophthalmology on July 1, 1954.

FREDERICK CARL CORDES, M.D.

Born, San Francisco, June 12, 1892
A.B., University of California, 1915
M.D., University of California, 1918
Intern, University of California Hospital, 1918-1919
Private Practice: July 1, 1919
Associated with Eye Clinic, Out-Patient Department, University of California Medical Center since 1919
Instructor in Ophthalmology, 1921-1928
Assistant Clinical Professor, 1928-1934
Associate Clinical Professor, 1934-1936
Clinical Professor, 1936
Chairman: July, 1934
Certificate: American Board of Ophthalmology, 1922

Civilian Consultant in Ophthalmology to Surgeon General:
United States Army since 1943
United States Navy since 1946
Consultant in Ophthalmology, State of California, Board of Public Health, 1949 to 1953
Consultant to National Society for Prevention of Blindness, 1949
Board of Directors, National Society for Prevention of Blindness, 1955
Associate Chief Examiner, National Board of Medical Examiners, 1948-54
Director, Ophthalmic Publishing Company
Trustee, Heed Ophthalmic Foundation
Member, American Board of Ophthalmology since 1939; Chairman, 1949; Consultant
Member, Subcommittee of Ophthalmology, National Research Council, 1943 to 1948
President, Pacific Coast Oto-Ophthalmological Society, 1939 (Member)
Association for Research in Ophthalmology, 1944; Advisory Member Publishing Committee, 1955
Pan-American Congress of Ophthalmology; Vice President, 1943 to 1952, now on Advisory Board
Member Executive Committee International Congress of Ophthalmology, 1954
Fellow, American College of Surgeons; Member Board of Regents, 1956
Member A.M.A., Chairman for Ophthalmology, 1945
California State Medical Society, Chairman (Ophthalmology), 1930
Council of American Ophthalmological Society, Chairman, 1949; President, 1956-57
American Academy Ophthalmology and Otolaryngology; President, 1953
San Francisco Ophthalmological Round Table; President, 1950; Chairman, nominating committee
Advisory Committee Variety Club Blind Babies Foundation; Chairman, 1955
Associate Editor, AMERICAN JOURNAL OF OPHTHALMOLOGY since 1929
Editorial Board of *California Medicine*
Trustee of Francis I. Proctor Foundation for Research in Ophthalmology
Honorary Member Society of Military Ophthalmologists, 1954
National Interprofessional Committee on Eye Care, 1951, 1954
Eye Research Fund, 1954 (myopia)
Member San Francisco Medical Society Press Consultant Panel, 1955
Committee of Museum of Ophthalmic History, A.M.A., 1955
Advisory Board, Pan-American Association of Ophthalmology, 1955
Member Editorial Board; *Archives of Ophthalmology*, 1944-1950
American Committee on Optics and Visual Physiology
Honorary Member New Orleans Academy of Ophthalmology
Fellow, California Academy of Sciences, October, 1957
Advisory Board, Knights Templar Foundation
Honorary Member, Association for Research in Ophthalmology
Honorary Member, Société Française D'Ophtalmologie, 1950
Honorary Member, Reno Surgical Society, August, 1956
Honorary Member, Cuban Society of Ophthalmology
Honorary Member, Mexican Society of Ophthalmology

THE CONTRIBUTIONS OF FREDERICK CARL CORDES, M.D., TO AMERICAN OPHTHALMOLOGY

JOHN H. DUNNINGTON, M.D.
New York

To portray clearly the contributions of Dr. Frederick Carl Cordes to American ophthalmology one must review briefly his career. Having been born, reared, and educated in California it is not surprising that his first contact with ophthalmology was at his alma mater, the University of California. Starting there in 1919 as an associate in the out-patient department, he moved rapidly forward to become chairman of the Department of Ophthalmology in 1934 with the title of associate clinical professor. Two years later he was promoted to clinical professor and continued as the executive officer of the department. Schooled in diligent study and possessing great administrative ability, he has created and organized an outstanding department. In it we find clinical problems intelligently presented by a corps of astute practitioners guided by this master clinician. Exacting in his demands, just in his criticisms, wise in his decisions, and prodigious in his efforts, he has welded together a group of loyal associates whose interest coincides with that of their able director, namely, the dissemination of knowledge on the clinical phases of ophthalmology.

To accomplish this end, well-organized seminars and short courses of instruction are conducted at frequent intervals, and to these gatherings come ophthalmologists from far and near. The orderly, concise manner in which the presentations are given reflect the meticulous nature of the director.

Not only has he been responsible for the development of this strong clinical department but he has also stimulated great interest in research. For many years he, single-handed, obtained funds to support the investigative activities of his staff. However, in 1946, with the great assistance of Dr. Phillips Thygeson, the assets of the Francis I. Proctor Foundation became available to this department. These funds along with others enabled them to build the Francis I. Proctor Laboratory for Research in Ophthalmology in which is housed most of their researches. At the official opening of this laboratory in 1954, noted scientists from all parts of the world assembled to participate in the sessions and to pay their respects to those individuals responsible for its creation. The outstanding achievements of the workers in this laboratory have brought additional honor and distinction to the Department of Ophthalmology.

These local activities have been but one part of Dr. Cordes' contributions to ophthalmology. In the State of California he has served as consultant in ophthalmology to its Board of Public Health, chairman of the section of ophthalmology of its medical society, and on the editorial board of *California Medicine*. He has been president of the Pacific Coast Oto-Ophthalmological Society and an active participant in the Los Angeles Study Club.

Nationally, he is a civilian consultant in ophthalmology to both the United States Army and the United States Navy and a director of the National Society for the Prevention of Blindness. He is the first ophthalmologist officially to represent ophthalmology on the Board of Regents of the American College of Surgeons, and is devoting much time and energy to this new responsibility because of his great desire to cement the ties of friendship between his specialty and general surgery. He has been chairman of the Eye Section of the American Medical Association and president of both the American Ophthalmological Society and the American Academy of Ophthalmology and Otolaryngology. For years he has participated freely in their executive and scientific deliberations. His sane judg-

ment, his intelligent discussions, and his willingness to help have made him a most valuable member of all of these organizations. He is also a member of the Association for Research in Ophthalmology, on the advisory boards of the Pan-American Association of Ophthalmology and the Knights Templar Eye Foundation, and a trustee of the Heed Ophthalmic Foundation.

In addition to these responsibilities he has served on the editorial board of THE AMERICAN JOURNAL OF OPHTHALMOLOGY since 1929 and at the present time is vice-president of its Ophthalmic Publishing Company. For six years he was also a member of the editorial staff of the *Archives of Ophthalmology*. A frequent contributor to the ophthalmic literature he is best known for the very careful, precise manner in which he prepares and presents his material, and for the clinical importance of his discussions. His report on "Failure in congenital cataract surgery: A study of 56 enucleated eyes," given as the XII Edward Jackson Memorial Lecture before the American Academy of Ophthalmology and Otolaryngology, did much to clarify this beclouded issue. His manual on "Cataract types" prepared for the Section on Instruction of the American Academy of Ophthalmology and Otolaryngology has long been of particular value to the younger members of the specialty. The ocular manifestations of diabetes mellitus, endocrine exophthalmos, and angiomatosis retinae are among other clinical subjects to which he has made noteworthy contributions.

His service to the American Board of Ophthalmology has been outstanding. Since becoming a member of its examining team in 1939 he has been a most conscientious and diligent worker. He has labored hard and long on its various committees, was its chairman in 1949, and has been a consultant since that time. Through his wise counsel and just examining, he has won the respect and admiration of colleagues and candidates alike.

In Dr. Frederick Carl Cordes are incorporated the ideals of a true physician. He has established a Department of Ophthalmology known for the excellent character of its clinical and research accomplishments. By his example as a teacher he has inspired others to give freely of themselves and by his writings he has portrayed in clear concise words the mature judgment of a wise practitioner. These achievements bespeak the value of hard work and unselfish devotion—two outstanding characteristics of this gentleman known for his integrity and for his insatiable zest for knowledge.

Along with all of these extracurricular activities Dr. Cordes has maintained an active practice and in his private office one finds further evidence of his organizing ability, his keen clinical judgment, and his patient understanding. Thus we see that this clinician had added greatly to the luster of American ophthalmology's star.

FREDERICK C. CORDES—TRUE PHYSICIAN

SALUTATION

It has been my privilege to have known Frederick C. Cordes for nearly 30 years. I did not know him during his formative youth but men who did have told me of those qualities which he exhibited at that time, qualities which have since characterized the man. One of his premedical classmates said to me: "I never knew Fritz to do a mean nor dishonest thing. He made mistakes, but they were honest mistakes; and he never resented criticism. As a student, as an athlete (he was a member of the first shell of the rowing team), and as a social associate, he was always a square shooter."

Cordes early realized the validity of the Oslerian dictum that one should never attempt the subsequent until he had mastered the preceding. As an illustration of this may be cited an incident that occurred about 1930. Walter S. Franklin, chairman of the Department of Ophthalmology, wished to retire. He recommended to the dean of the School of Medicine that Fred Cordes be named to succeed him. To everybody's amazement, Cordes declined on the ground of his comparative youth and unattained maturity. He preferred to continue in a secondary capacity. Thereupon, another man, the late Joseph McCool of Portland, Oregon, was named; and, for several years, Cordes worked on with industry and obvious dedication. With McCool's retirement, he was designated chairman in 1934.

During its formative years, the department was housed miserably in overcrowded and obsolete quarters in the first-constructed building on the medical campus. The staff was inadequate, technicians almost nonexistent. Even after Cordes had attained status, he personally embedded, sectioned, and stained his own specimens, many of which are still in use. In addition, he brought home various specimens from his trips over this country and abroad, rare and valuable specimens which are of great teaching value.

Among Dr. Cordes' confreres in other departments, one often hears comments about his industry. In fact it has become something of a campus joke that "Fred never has any difficulty in finding a place to park his car, for he is on the hill in the morning before seven, and before the rest of us get here." The usual spectacle of the ophthalmologic staff trailing along behind the Chief to the campus cafeteria for an eight-thirty seminar, has produced many a knowing smile.

For more than two decades, it was my lot to act as Director of the Out-Patient Clinics —a position of which some took a dim view because of the fact that occasional clinicians are afflicted with the prima donna complex; but never did I experience difficulty from the Department of Ophthalmology. Many of our patients are referred to us by practitioners in the smaller communities all over the West. These patients are poor, and the cost of staying in San Francisco during the course of our studies is often onerous. How often have I seen the Ophthalmology Department change its routine, often at a trying disadvantage, in order to shorten the time of the patient's stay. And how prompt were the reports to the referring doctor. Even the novitiates, their minds on other things, soon came into line; for the Chief's wishes were well known. Furthermore, there was the occasional patient, too proud to accept free clinic care, one who wished to pay a small sum, even pitiably inadequate, to a staff man in his private office. Never was co-operation refused, even if the token fee failed to meet the operating costs. But it allowed the patient to retain his proud self-respect—and that is of the very essence of good medicine.

Cordes' ability to seek out and encourage men of promise and to aid them in every possible way, to inspire them to do their very best, and finally to assign them to various posts, at home and abroad, is outstanding. The quality of such men as Campion, Crawford, Dickey, Harrington, Hogan, Shaffer, to name a few, is indicative of this virtue.

It is a long step from today's postdoctoral instruction to the time when the general practitioner, tired of his routine, prepared himself as best he could by going abroad and taking a cram-course, and thereafter became a specialist—in ophthalmology for example. In specialist training, Frederick C. Cordes has taken his place in the vanguard. His program of a three-year residency in ophthalmology is admirable. Young men with records of premedical high scholarship, whose general internships have been flawless, and who desire to continue in ophthalmology are chosen, four each year, for a three-year course. By staggering the entries, there is a continuity of effort and achieve-

ment, the students learning from each other, as well as from the regularly constituted staff. Over the years, never once has a man, so trained, failed to pass the national examining board. The Department of Ophthalmology has done its part, and more, in the regularly offered refresher courses for practicing doctors, given by the School of Medicine.

Remarkably admirable is Cordes' ability to inspire and advise persons of wealth, who may wish to make contributions to life by way of endowments, particularly in the fields of research. The Proctor Foundation for Research in Ophthalmology in the University of California Medical Center in San Francisco is a notable example.

Cordes has been successful in obtaining fellowships for foreign students who wish to study here; and for our own students who desire to study abroad. The medical, social, and even political advantage of such procedures is well known.

Frederick Cordes started writing early, even in the days of poor quarters and crowded laboratories. The frequently heard pleasantry that "the last paper that a scientist writes is a description of his new laboratory," has never applied to him. One has only to glance at the bibliography herein to realize the continuous stream of titles that have flowed from his pen. They began in the twenties and are now at full tide in the fifties. Indeed, they cover the field of ophthalmology, and they are consistent with the inquiring and ripening mind.

Nor has he been slothful in furthering the development of his specialty, both at home and abroad. Medical meeting attendance and participation have been consistent. Other faculty members of this School of Medicine and Medical Center count themselves fortunate in having such an admirable confrere. Long may he survive, the better to aid in the molding of the minds of the young.

W. E. Carter.

Salutation

My association with Dr. Frederick C. Cordes began in 1926, when, as a brash young eye physician with two years of postgraduate work at the Graduate School of the University of Pennsylvania, I was invited to continue my studies in the office of Dr. Walter Scott Franklin, professor of ophthalmology at the University of California Medical School, and his associate Dr. Cordes, then an instructor in the same institution. Fred was exceedingly kind to me and in a quiet and unobtrusive way did everything he could to make my path easier. I mention this because I soon learned this was a characteristic of Fred's—to make things easier for others while remaining in the background himself. This contributes to his great success as a teacher of men whether they be medical students, residents, or ophthalmologists returning for a refresher course.

His own eye training was acquired the hard way. His preceptor, Dr. Franklin, head of the Eye Department at the University was an outstanding clinician but a critical taskmaster. Fred learned his basic science by digging it out by himself in his free hours. This meant, for example, learning eye pathology in a little laboratory he set up himself in the old medical school building, where he began his day at 6:00 A.M.

After the retirement of Dr. Franklin and then of his successor, Dr. Joseph McCool, Fred was appointed Chairman of the Eye Department, in 1934. He then held the rank of associate clinical professor. He became clinical professor in 1936.

The Eye Department at the University of California, recognized as one of the great eye departments of the United States, is a monument to his persistent and tireless efforts. He initiated the residency program in

1928 and expanded it from one trainee for one year, to 12 residents for three years each. Young physicians from all parts of the country, and from Europe as well, now seek the privilege of working under him and his associates. He also started the postgraduate teaching program which has become a great part of our department and attracts eye physicians from all over the United States.

By personal example he attempts to influence his associates in the department to do original thinking, research, and good scientific writing. He personally found the funds and the space and the men to start a separate Eye Pathology Laboratory for the department. You are all familiar with the growth of his laboratory under the able direction of Dr. Michael Hogan. Because of Fred's untiring efforts and foresight the Francis I. Proctor Foundation for Research in Ophthalmology was located in San Francisco at the University of California Medical School. It must be a source of great satisfaction for him to see how under his chairmanship the department has expanded from a relatively small part of the university, to the high place it now holds both nationally and internationally. This growth is the result of his love of teaching young men, students and graduates, and of his interest in research, and particularly his skill as an organizer and a leader. He has shown imagination and enterprise and, what is especially important, tact in the conduct of his department, and those of us fortunate enough to be associated with him are often astounded at his foresight in formulating the policies of the department. We particularly admire his persistent determination to make things better. Nothing is ever "good enough" for Fred.

Teaching students was an essential part of his life, starting with medical students, then residents, and then postgraduate students. Finally it was natural that he was selected for membership on the American Board of Ophthalmology in 1939. He has served on the board continuously to date, having been elected to chairmanship in 1949, and finally to consultant which position he now holds.

A steadily growing number of young men have acquired their training at the hands of Fred and his associates. He is a good clinician, an inspiring teacher, a tireless worker, and above all a leader and organizer. His interests are varied and, in addition to his regular duties as department chairman, he has served with distinction on the library committee and many other committees of the university. As a result of his efforts this year the Franklin Memorial Eye Library will be dedicated as a tribute to Fred's first teacher. He has a real love for books and over the years has collected a fine library of books dealing with California, its history and its people.

This is but one of his many hobbies, and it would be difficult to say which is his major one. In addition to collecting Californiana he collects old medical books and anyone who has seen his library will be impressed by its scope. He builds scale model sailing ships and so good are they that the famed De Young Museum asked him to build a model of the Gjoa, Amundsen's ship that first sailed the North-West Passage, for its permanent collection. Incidentally he earned his letter at the University of California by rowing bow oar on the varsity crew which may explain his interest in boats. Another of his interests has been photography which may account for the fact that one of the first fundus cameras in the West was the one in the eye clinic at the University of California. Being a normal human being he has to admit to one defeat—golf. The less said about this the better. He is not one to give up on a hobby once he becomes interested. This applies to stamps, books, photography, ship models, ophthalmoscopes, and so forth.

I know of only one exception. While in college he became interested in clocks, one in particular, the big clock in the tower at the old University of California Medical

School. It was rumored that the clock could strike the hours, but in deference to the people who lived all about in a quiet residential section of the city, the striking mechanism had been disconnected. Fred, aided by two willing classmates, climbed the old clock tower and, after working three nights, succeeded in restoring the sounding mechanism and barricading the approach to the tower from the night watchman. Something was wrong with the wiring, however, and the complaints of the neighbors were many as the clock struck double the number of hours—which was most annoying at midnight.

Another of his hobbies is his collection of old ophthalmoscopes. This collection is now on permanent exhibition in the library of the medical school. Over the years he has added to this collection and it is rapidly becoming one of the most complete in the United States. To illustrate his versatility he has worked at theatrical make-up for the Bohemian Club of San Francisco for the past 20 years. He was director of the group responsible for this activity for many years. He has become such an artist that his services are sought by many amateur theatrical groups in this area, and for several years he worked with the professional make-up men for the San Francisco Opera Association.

An appreciation of the scope of his interest is shown by a review of a list of his publications. That his talents are not unrecognized is shown by the positions he has held in our national societies. His interest in these societies has never waned, and in fact seems to increase as he grows older.

National honors and recognition have given him an enviable position in American medicine and the University of California is proud of so distinguished a colleague. His active participation in medical education, his wide experience, and the catholicity of his interests, have given him, as chairman of the Eye Department for these many years, the ability to direct with special proficiency the diverse activities of the department and to make its contributions to the Medical School so outstanding; under his leadership this department had added luster to the entire school.

To those of us invited to participate in the preparation of this *Festschrift,* has been accorded a signal honor. It has given us an opportunity to pay tribute to one who has been a great credit to his alma mater, and one who will be long remembered by his many friends, his colleagues, his grateful patients, and especially by the many young men he has trained to become good eye physicians.

Joseph W. Crawford, M.D.
Clinical Professor of Ophthalmology,
University of California Medical School.

Salutation

"The ultimate accomplishment of a thinker is found not in his books nor in his opinions, but in the minds of men." This statement of Felix Frankfurter on Mr. Justice Holmes applies with even more force in the case of a teacher such as "Fritz" Cordes. No finer measure of Dr. Cordes' accomplishment in the field of ophthalmology can be found than the host of students he has trained and the colleagues he has influenced who now join in paying the highest form of tribute which a scholar can receive in the presentation of *Festschrift* as a token of their respectful admiration and gratitude.

The School of Medicine of the University of California is justly proud of Dr. Cordes' many accomplishments and particularly of the distinguished leadership he has given for so long to its Department of Ophthalmology. By industry, great energy, perseverance, and, above all, with superlative judgment and vision, he has built a great department,

perfectly balanced in its emphasis on the clinic and on research. These words have been chosen with care and represent no empty eulogy, as all of his colleagues will testify. If I were asked whence came Dr. Cordes' understanding of his field, I would quote his favorite poet, Goethe: "Man lernt nichts kennen als was man liebt."

As spokesman for his fellow faculty members and for his school, it is a pleasure to acknowledge our great debt to Dr. Cordes and to extend greetings.

J. B. deC. M. Saunders,
Provost,
University of California
San Francisco Campus.

October, 1958

Salutation

Civilized society is the product of human effort, of the work of human brains and hands. What progress man has made over the centuries has been possible only by work. It is work that has lifted mankind out of the depth of savagery. While Dr. Frederick C. Cordes has probably never phrased his life philosophy in just these terms, there is no doubt in my mind that this is the code by which he has lived, and the wellspring of his very considerable achievements.

As much or more than any other member of the faculty of the University of California that I have known in the past 45 years, Dr. Cordes is entitled to repeat the words of Amiel, "What I want is work, for it is work that gives flavor to life." Throughout his long academic and professional career he has shown himself to be an individual with a rare combination of traits, an unusual practitioner of the art and science of medicine, a teacher who combined a prodigious curiosity with a love of imparting his knowledge to others, and whose native generosity of spirit led him to sacrifice a large portion of his time in relatively unremunerative, although personally rewarding, pursuits.

All of these characteristics of Dr. Cordes, plus one other catalytic ingredient—a deep-rooted humanism—have given his life and his career a larger meaning than even his generous abilities could otherwise have achieved. As a result of this happy conjugation of personal qualities, the Department of Ophthalmology, of which he is chairman, has come to be a bright star in the constellation of the School of Medicine in San Francisco, and he and his colleagues and students have brought fame and honor to the University of California as a whole.

For all these reasons, and for others more personal, I am delighted to be privileged to take a small part in this salute to Dr. Fred Cordes, a distinguished teacher and researcher, a true physician, and a steadfast friend.

Robert G. Sproul,
President Emeritus,
The University of California.

Fred Cordes: Gentleman and Scholar

This is a tribute to Fred Cordes, which I have hesitated to write because it may not be sufficiently praiseworthy in extolling his many virtues or, on the other hand, it may err in being too fullsome. Others have covered his scientific achievements, his national activities, his college life, and his medical school career. It falls to me to write about the man himself; a man whom I have known and respected for the past 20 years.

When I first met Fred, back in 1939, it was at a professional football game. I shall always remember his enthusiasm for the sport; an enthusiasm which has continued

ever since. At various national meetings over the years, when an opportunity arose which did not interfere with his committee duties, Fred would be off to a Saturday afternoon game, especially if his favorite California Golden Bears were playing anywhere nearby. If attendance was impossible, the game was followed closely on the radio. A frank partisan, he was, nevertheless, always the first to applaud brilliant play by the opponents. This is in keeping with his character as shown in his relations with his confreres. A severe judge perhaps, but a kind one with no meanness in him, meting out criticism when justified but eager to praise when praise was due.

Early in his career he displayed the qualities of leadership to a marked degree. This trait, coupled with absolute integrity and devotion to duty, have stamped him as an outstanding person in ophthalmology. But let no one think he has no outside interests!

It is a little difficult to catalogue all of his nonprofessional activities because there are so many of them. His hobbies are legion. As one of his fellow citizens told me "he rides a hobby until he has just about exhausted its possibilities and then starts a new one, without, however, ever quite giving up the old one." His determination to carry through with plans, despite all obstacles, is exemplified by his collection of old ophthalmoscopes, said to be one of the best extant. It is typical of Fred that, not being able to obtain one of Helmholtz's original instruments, he constructed one himself from a study of the original article. Needless to say, this replica was exact in every detail, as proven later when he finally did obtain an original.

This habit of collecting and preserving valuable objects of historical interest began many years ago. His first attempt was stamps, especially United States stamps. By now, this collection is enormous and of considerable value.

Another great hobby is his ship-model collection. I have gazed with admiration on this on several occasions. Some of them are good enough to be in the Maritime Museum in San Francisco. Such a one is his model of the "Gjoa," the small sealing sloop used by Amundson in 1906 in his discovery of the Northwest Passage. The original ship happened to be in Golden Gate Park and Fred spent many hours measuring her completely, reducing her to scale and then constructing this beautifully accurate model. Another masterpiece is his model of the brig "Pilgrim," which Dana described in 1840 in his "Two Years Before the Mast." This model was constructed entirely from descriptions found in the book; a truly remarkable feat.

Fred's intense interest in the history of his native state has resulted in a remarkably fine private library on the subject. He has collected everything about it, facts and legends, native birds and flowers, old landmarks, and so forth. He can talk with authority on such subjects as the Spanish missions and the Gold Rush. I was once enthralled at his recital of the attempt by the Russians, coming down from Alaska, to establish a colony about 70 miles north of San Francisco in the early 1800s. The colony only lasted a few years but the old Russian museum was still preserved and Fred knew everything in it. I shall never forget that delightful afternoon, standing on this historic spot with a real expert leading me step by step down the paths of California history. I suddenly realized what a true scholar he was and how much I had to learn.

For many years photography has been one of Fred Cordes' greatest hobbies. Every known photographic gadget is employed. Being a true perfectionist, it is his custom to take three shots of a good subject, one of which he thinks is correct, one "over" and one "under" exposed. Later he will keep the one which turns out the best and discard the other two. Needless to say, his pictures are superb.

One social organization especially dear to his heart is the Bohemian Club of San Francisco. For many years he has been one of its most devoted members, always attending the annual encampment in the beautiful redwood

grove. Here he has been prominent in helping put on their excellent plays, since he is an expert in stage makeup! This last accomplishment is probably not well known to his colleagues in ophthalmology but he is so good at it that for many years he acted as part of the makeup crew for the San Francisco Opera Company.

Those of us who have had the good fortune to be his guest realize what a superb host he is, generous to a fault without any ostentation, kind and affable. A lover of a good story and a connoisseur of California wines, a more delightful companion cannot be found.

These words have been penned in praise of the man and to make some readers cognizant of his many accomplishments outside the field of ophthalmology, of which, perhaps they were not aware. What can we say now on the debit side, since, after all, no one is perfect? Well, very little I think. He has his peculiarities like everyone else—a bit of a slave driver in wanting to get things done as soon as possible. But this, after all, is a necessary quality for a good leader and those of us who have served on committees and symposia of which he was chairman have realized how important it was to have such a strong hand at the helm.

No profile of Fred Cordes would be complete without reference to his mania for being on time, especially when catching trains and airplanes. More than once he has delivered a visitor at the station or airport one and one-half hours before departure time; but no one ever missed his transportation!

This versatile man is known as a great collector but I venture to guess that the collection that means most to him is his collection of friends. On this no tangible value can be placed but I am sure he values them as much as they value him.

Edwin B. Dunphy,
Harvard Medical School.

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Frederick C. Cordes, M.D.

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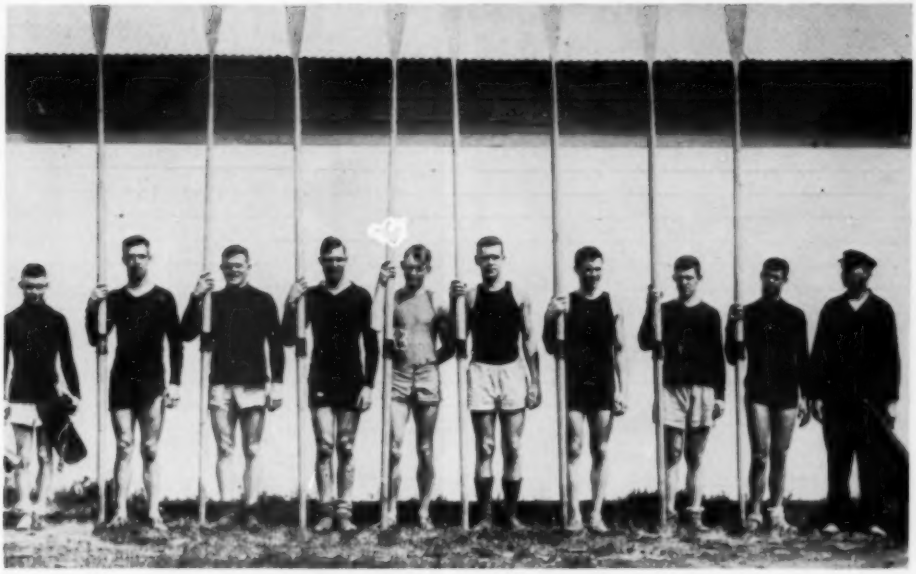
F. C. C. EXTRACURRICULAR

A faithful friend is a strong defense: and he that hath found such a one hath found a treasure. *Ecclesiasticus* VI:14

It is rewarding to see Fred Cordes honored in this Festschrift by his friends, associates, and colleagues on the occasion of his 67th birthday and his elevation to emeritus teacher. Elsewhere in this issue will be found the descriptions of his many useful activities and contributions to our science. Here I should like to present other facets of his versatile character, from the viewpoint of an intimate friend of some 30 years.

Fred has been an associate editor of THE JOURNAL since 1929. In this time he has contributed much to its amazing success by his sound advice and aid both as editor and director. His common-sense editorials have been widely appreciated. Here, as in all of of his activities, he shows the fundamental honesty, integrity, and sincerity of his character. Never impulsive, he can always be relied upon to devote much thought and consideration to any problem, before expressing his opinion as to its answer. It is this quality of his makeup that has contributed so much to his success as a clinician, administrator, teacher, writer, and lecturer, but above all as a friend and boon campanion. You can count on him, always.

Fred is a gregarious person with a quiet sense of humor. His greatest joy has been his membership in the Bohemian Club in San Francisco. He is very active in this famous organization, especially during its annual summer encampment in the "Grove," a forest of giant redwoods north of San Francisco. Here he and a number of his boon companions have a camp of their own called "Land's End." Fred has shared the pleasures of the Grove with many of his close friends in ophthalmology as his guests from time to



A port oar. University of California crew, 1915. Number 2, F. C. C.

time, and those of us who have had this privilege have always remembered the occasion, the "High" and "Low Jinks" the other ceremonies and informal visiting around the other camps, with great pleasure. At the moment, Fred is chairman of the Grove Committee, a position of considerable responsibility that he fulfills with his usual efficiency. He has also been, for many years, one of the "make up" artists whose job it is to adjust the faces of those taking part in the plays throughout the year in the Club itself and at the Grove. It requires a certain amount of skill to make a bearded pard look like a charming miss of the chorus, and Fred's results are indeed remarkable in this line, perfectionist that he is.

Another of his pleasures is the making of ship models. He has finished a dozen or so of these in the last 20 years, working from blue prints with exact scale and himself casting the metal parts that may be required. The models are beautifully and meticulously done, each a work of fine art, requiring most delicate skill, such as an ophthalmic surgeon should have. One of his first models is that of the *Gjöa,* Ronald Amundsen's 47-ton sloop in which he made the Northwest Passage in 1903-1906. Amundsen purchased this small cargo boat in 1901 in Hardanger Fjord, Norway. It was then about 30 years old. He strengthened and sheathed her in oak, loaded her with Arctic supplies until the water line was at her deck level. A two-cylinder naphtha engine saved her in tight spots.

The expedition of seven men left Disko, Greenland, in July, 1903. Three winters were spent in the ice before it arrived at Nome, Alaska, in 1906. The journey ended in San Francisco, when in 1909 she was hauled out and presented to the city. Falling into disrepair, the *Gjöa* Foundation was formed to restore her and reconstruction was completed in 1949. Fred's imagination was aroused and his beautiful model was presented to the museum in the Golden Gate Park where it occupies a prominent spot and can be readily seen along with the *Gjöa* itself. The other models he has made are worthy of being called museum pieces too.

Fred has a fine collection of rare books on

Phyllis and Stewart Duke-Elder in the Bohemian Grove, 1946.

Grove friendships. F. C. C. and L. T. P.

Grove friendships. F. C. C. and A. B. R.

Grove friendships. F. C. C. and Walter S. Atkinson.

early California, for his love of his native state is a strong part of his fiber. In 1934 he was reading a rare book catalogue and came across a title, *Der Staat Californien in Medicinisch-geographischer Hinsicht* by Dr. J. Praslow published in Göttingen in 1857. He sent for this item and decided to share his delight by translating and publishing it. It is a book of 86 pages, beautifully printed. It was published in 1939 in San Francisco by John J. Newbegin, and is now a collector's item. It is great fun for the physician reader.

He is widely known for his superb photography, medical and otherwise. The showing of his colored slides is always a treat for the beholder and Fred has been most generous in sharing this pleasure with others. Woe betide any of his residents who show slides that are dirty or have fingerprints on them. His scientific papers are prepared with meticulous care and he spends hours rehearsing his presentation so that each one is a gem of coherent thought and lucid expression. He has had great influence on the young men in our societies in this respect.

There's nothing to this.

Yes, doctor.

So we see that Fred is indeed a versatile and many-sided man, excelling in his professional work, in his hobbies, and in his capacity to make loyal and life-long friends. His retirement from active teaching and the labor of administering one of the outstanding departments of ophthalmology in this country, for which he was chiefly responsible, only means the giving up of some burdens. But this will permit him the leisure to assume others, for you can rest assured that he will never be idle.

We salute him and wish him well as an emeritus and would have him know that he has the affection of a host of professional and lay friends.

Derrick Vail.

CYCLOTRON CATARACTS*

ALAN C. WOODS, M.D.
Baltimore, Maryland

In December, 1948, it was discovered that five nuclear scientists who had been exposed to cyclotron irradiation had developed incipient lens opacities. Since it was known that the cyclotron produces fluxes high in fast neutrons and hard gamma rays, this observation immediately introduced the question of what role fast neutrons might play in the production of radiation cataracts.

It had been known almost since the discovery of X rays that undue exposure to ionizing radiation frequently resulted in the late development of characteristic cataracts. It was then generally believed that comparatively large doses were necessary to produce these changes. However, Hunt[1] (1947) estimated the threshold dose might be as low as 500 to 1,000 r, and Cogan's[2] studies (1950) indicated that the lens was susceptible to the usual X-radiation used in therapy, and that cataracts might result from doses as low as from 600 to 1,000 r. The recent clinical study of Merriam and Focht[3] of 100 patients with radiation cataracts places the threshold cataractogenic dose for man more exactly. In patients receiving a single treatment, the minimum cataractogenic dose was 200 r; in patients receiving divided treatments over a period of three weeks to three months, the minimum dose was 400 r; in patients receiving divided treatments for more than three months the minimum cataractogenic dose was 550 r. In patients receiving 750 to 950 r on a three weeks' to three months' period, 60 percent developed cataracts, and in 50 percent the opacities were progressive. The authors further found that the higher the dose, the shorter was the latent period and the higher the incidence of progressive lens changes.

It was known that there was a relatively high incidence of lens changes among the survivors of the atomic bombing of Hiroshima and Nagasaki. Early observations had indicated that the majority of the patients with cataracts had been within 3,000 feet of the hypocenter. Later studies revealed that the greatest distance from the hypocenter at which lens damage could be definitely established was 3,600 feet or 1.97 km. Since the amount of neutron irradiation at this distance was considered negligible, neutrons were not incriminated in these atom bomb radiation cataracts.

It was also known that in 1945 and 1946 10 scientists had been the victims of an accidental exposure to cyclotron irradiation at the Los Alamos Scientific Laboratory. Two of the survivors later developed irradiation cataracts. In both there was a definite latent period, the lenses being clear in 1949.

Therefore, while a great deal was known of X-ray cataracts, little was known of the role neutrons might play in their production. In the light of the discovery of the lens opacities in the eyes of five scientists exposed to cyclotron irradiation and the probable high importance of lens changes in atomic bomb survivors, the Atomic Energy Commission enlisted the aid of the National Research Council in an investigation of cyclotron and atomic bomb radiation cataracts. A Committee on Radiation Cataracts was appointed, which met for the first time at the National Academy of Sciences in January, 1949. The investigation of the problem was now organized on various lines. In the summer of 1949, a team under Dr. Cogan went to Japan to study the lens changes among the Japanese survivors of the atomic bombing, similarly Dr. Donaldson went in 1950, and Dr. Sinskey in 1953. A great amount of experimental work was initiated on the subjects of the effect of

*A report written for the National Research Council and cleared through the National Research Council and the Atomic Energy Commission.

X-ray and gamma radiation, and thermal and fast neutron irradiation on the lens of mice and other laboratory animals. At subsequent meetings of the Committee on Radiation Cataracts, this work was reviewed, summarized, and reported. In 1953, W. T. Ham[4] made an exhaustive review of the literature and summed up these investigations to that date. Reference should be made to this excellent treatise for details.

In addition to sponsoring these field and laboratory investigations, the National Research Council undertook to arrange for the periodic examinations of the eyes of the scientists who had been exposed to cyclotron irradiation. These examinations were conducted by a panel of ophthalmologists appointed by the Committee of Ophthalmology of the National Research Council and were held in the Wilmer Institute of The Johns Hopkins Hospital on January 18, 1949; February 24, 1950; April 2, 1951; January 21, 1953; March 14, 1955; and January 4, 1957. The original panel consisted of Dr. A. B. Reese, Dr. J. S. Friedenwald, and Dr. A. C. Woods. Dr. Reese dropped out after the 1953 meeting, and Dr. Friedenwald died in 1956. Dr. A. E. Maumenee and Dr. Woods conducted the final examination in 1957. At all examinations the panel was assisted by members of the resident staff of the Wilmer Institute. Full notes of these examinations were recorded. The purpose of this communication is to report the results of these examinations.

The various patients, all of whom were trained physicists, made every possible effort to estimate the type, the amount, and the duration of their exposure to cyclotron irradiation. As pointed out by Dr. Ham, little reliance can be placed on the laboratory records several years old and on pocket dosimeters and film badges designed primarily to detect gamma rays. These estimations, therefore, represent little more than educated guesses by well-qualified physicists who were handicapped by incomplete laboratory records and faulty instrumentation as far as neutron dosimetry was concerned. These estimations on the first group examined were summarized and reported by Abelson and Kruger[5] in 1949.

At the first examination in January, 1949, 11 physicists who were thought to have been exposed to cyclotron radiation were examined. Seven of these (No. 1, 2, 3, 4, 6, 8, and 11 in table 1) were found to have lens changes. Each of these gentlemen, with the exception of No. 2, were examined at all subsequent sessions. Patient No. 2 dropped out after the 1953 examination, but a final record of a 1957 examination by Dr. Reese has been obtained. In 1950, four additional physicists (No. 5, 7, 10, and 13) were examined. All of these men (with the exception of No. 7 who missed the 1951 and 1953 examinations) were present at all subsequent examinations. In 1957, two additional men (No. 9 and No. 12) were examined. There are therefore a total of 13 patients with cyclotron cataracts whose histories are available for analysis, and in 11 of these there are repeated ophthalmologic examinations over a seven-year period.

At the first examination the family history of ocular and systemic disease, the past medical history, and the story of the present ocular difficulty was recorded. Each ophthalmic examination was complete and included examination of the external eye and adnexa, the ocular movements, pupillary reactions, ocular tension, visual fields, the opthalmoscopic examination with dilated pupils, a detailed slitlamp examination, and a refraction examination with a record of the uncorrected and corrected vision. Each patient was individually examined by each member of the panel, and a group opinion was recorded with any additional comments from the individual examiners.

Except for the changes in the crystalline lens, no pathologic changes in the eye attributable to the effects of radiation were found. One patient (No. 1) showed a corneal scar which had resulted from a prior traumatism. This same patient showed a small spot of

TABLE 1

SYNOPSIS OF RESULTS

Number Age in 1949 (yr.)	Date + Amount of Exposure to Cyclotron Radiation	Onset of Visual Failure or Discovery of Lens Opacities	Latent Period between Exposure and Lens Opacities (yr.)	Lens Pathology 1. Examination						Other Ocular Pathology	Progression of Cataracts	Operations	Final Results (1957)
					Ant. Cortex	Nucleus	Post. Cortex	Vac.	Iridescence				
No. 1 30	1947–48 30–100 rad over 30 wk.	June 1949	1	R	+	0	++	+	+	Corneal scar in left	Rapid—6–8 mo. each eye	R. July 1949 L. Feb. 1950	R. successful, 20/20 L. lost postop. epi.-endo. dystrophy
				L	0	0	+	+	+				
No. 2 36	1944 acute exp. 120 rad. 1945–49 100 rad	Sept. 1946	2½	R	+	0	+++	0	0	None	Rapid—10 mo. each eye	R. Mar. 1954 L. June 1947	R. successful, 20/15 L. lost postop. endophth.
				L	operated in 1947								
No. 3 42	1943–44 80 rad over 25 wk.	March 1946	2	R	+	0	++	0	0	None	Slow in both eyes	R. Nov. 1952	R. successful, 20/15
				L	+	0	+	0	0				L. 20/30
No. 4 26	1943–44 80 rad over 25 wk.	Early in 1946	2	R	+	0	+++	0	0	None	R. rapid (1 yr.)	R. Mar. 1949	RV 20/15
				L	+	0	+++	0	0		L. slow (2 yr.)	L. June 1950	LV 20/15
No. 5 32	1945–49 80–120 rad over 250 wk.	Nov. 1948	3	R	+	0	+++	0	+	None	Rapid both eyes (1 yr.)	R. Feb. 1951	RV 20/25
				L	+	0	+++	0	+			L. June 1951	LV 20/20
No. 6 47	1943–44 65 rad. over 25 wk.	Oct. 1948	4	R	0	0	+	+	+	None	R. moderate	None	RV 20/50 /
				L	0	0	+	+	+		L. none		LV 20/20
No. 7 39	1946 acute 45–50 rad (left side)	1949	3, R.E. 5, L.E.	R	+	0	+	+	+	None	None	None	RV 20/15
				L	+	0	++	+	+				LV 20/40
No. 8 32	1941–1947 30–40 rad over 250 wk.	Sept. 1948	3(?)	R	0	0	+	+	0	Benign melanoma L. fundus	R. none	None	RV 20/20
				L	0	0	+	0	0		L. slow 1949–50		LV 20/40
No. 9 32	1942–49 ?	Aug. 1955	6(+?)	R	+	0	+	0	0	None	None or slight	None	RV 20/30
				L	0	0	+	+	0				LV 20/30
No. 10 23	1946–49 78 rad over 150 wk.	Oct. 1949	2(?)	R	0	0	+	0	+	Drusen in both fundi	Slight 1950–51; none thereafter	None	RV 20/20
				L	0	0	+	0	+				LV 20/15
No. 11 33	1947–48 30–100 rad over 10 wk.	Jan. 1949	2	R	0	0	+	+	++	None	Very slight over 8 yr.	None	RV 20/20
				L	0	0	+	+	++				LV 20/20
No. 12 33	1942–43 very slight	1956 (discovered on routine examination)	(?)	R	+	0	+	+	0	None	None	None	RV 20/15
				L	+	0	+	+	0				LV 20/15 –
No. 13 35	1943 "negligible"	1949 (discovered on routine examination)	6(?)	R	0	0	+	+	0	None	None	None	RV 20/15
				L	0	0	+	+	0				LV 20/15

retinal atrophy above the fovea, which might have been the result of a petechial hemorrhage. Another (No. 8) had a benign melanoma of the choroid which was unchanged over the period of observation and which all examiners agreed was congenital. A third patient (No. 10) showed a few drusen bodies over the optic nerve and in the perifoveal areas, but there was no reason to believe these were out of the ordinary or in any way attributable to the effects of radiation. Except for these isolated conditions, and the results of operation, there were no abnormalities of any kind discovered in the eyes or ocular adnexae.

The lenticular changes which followed exposure to cyclotron radiation all followed the same general pattern as do cataracts secondary to the gamma rays of radium or X rays. There was a prolonged latent period between exposure of the eyes to the neutrons and the development of the lens opacities. In the 13 cases in this study the minimum interval from the last exposure to neutrons to either a conscious visual failure, or the discovery of early lens opacities on routine examination, was one year (No. 1), while the maximum time between exposure and the development of cataracts was probably over six years (No. 9). Since it is not known whether the lens damage was the result of one specific exposure to neutrons or to the cumulative amount received, it is impossible to fix the length of this latent period more exactly than from one to six years. On the average, as shown in Table 2, the more severe the exposure, the shorter the latent period.

While the data available from this series of patients give only an approximate idea of the latent period between exposure to neutrons and the onset of lens changes, they do give a clear picture of the development of the resultant cataracts. The first changes occurred in the posterior, subcapsular cortex. These consisted of a few tiny whitish dots. In a few cases there was no progression. In the progressive cases these dots increased in number and in size, and gradually assumed a rosette or disciform configuration between the posterior capsule and the nucleus of the lens.

In these early stages of development it was specifically noted that the posterior capsule was not involved, a clear zone being visible between it and the opacities. In the later stages, as the opacities increased in size and density, they spread backward toward the posterior capsule which then could no longer be visualized. In only one patient, with a nonprogressive cataract (No. 10), was a small opacity identified in the posterior capsule itself. All examiners believed this to be a congenital phenomenon. In

TABLE 2

ESTIMATED DEGREE AND DURATION OF EXPOSURE IN RELATION TO LENS CHANGES

Degree of Lens Damage	No. of Eyes	Estimated Neutron Exposure	Average Duration of Exposure	Latent Period between Exposure and First Lens Opacities	Progression of Lens Opacities
1. Minimal—vision not affected	10	Varied from "minimal" in two patients to a possible maximum of 78 rad. in one	One acute (slight) Range 25–250 wk Average 2 yr	4.5 yr.	None
2. Slight—vision reduced but not below 20/30	3	Average—40 rad.	One acute (est.) 40 rad. in 1 yr. Slight over 5 yr.	4.0 yr.	Slight for 2 yr. Thereafter stationary
3. Moderate—vision reduced to 20/40 or less	4	Unknown in two 80 rad in one	1.5 yr.	3 yr.	Moderate 2 yr. Thereafter stationary in two Slow in one
4. Severe—all eyes operated cataracts	9	80 rad	One acute Average of others 1 yr.	20 mo.	Rapid in four (6–12 mo.) Slower in four (18–24 mo.) Slow in one (4 yr.)

about one half of the cases these posterior cortical opacities had a golden hue or iridescence. In the progressive cases, whitish, dot-like opacities later appeared in the anterior cortex, usually one to two years after the first posterior changes, but these never reached the number or density of the posterior cortical opacities. In no case was the nucleus or the anterior capsule involved.

Vacuoles in the lens were one of the first changes observed, and their presence in large numbers was specifically noted in nearly all of the early cases. In the advanced cases, which came to operation, vacuoles were noted in only two of the five patients. They were probably obscured or masked by the dense opacities. Visual failure was invariably due to the blocking of the pupillary space by the spread and increase in the density of the posterior opacities. In these cases the lens clouding often appeared to mushroom forward from the depths of the posterior cortex and up to the posterior portion of the nucleus, with a concavity on the anterior surface of the doughnutlike opacity.

In five cases the opacities progressed slowly for the first two years after the initial discovery. Thereafter, they remained stationary. In one patient (No. 11) they progressed very slowly during the entire eight-year period of observation, but not to the point they caused any serious impairment of vision. In two patients, after the original discovery of minimal opacities, no progression of any kind was noted.

In the remaining five patients, the opacities became so dense that all useful vision was lost and operation for extraction of the cataracts became imperative. Four of these (No. 1, 2, 4, and 5) had bilateral cataract extractions performed, while one (No. 3) had a unilateral extraction only. In two patients (No. 1 and 2), the cataracts developed with considerable rapidity, the interval between the initial visual loss and practical blindness being less than one year. In two patients (No. 4 and 5), the progression of the cataracts was slower, the interval between onset of visual loss and blindness being 18 months to two years. In only one did the progression extend to four years.

The nine cataract extractions were all done by ophthalmic surgeons of great skill, in whose hands an incidence of 90 percent successful intracapsular extractions could reasonably be expected. It is notable that in only four instances were intracapsular extractions successfully performed. In two instances the operating surgeon noted undue adherence between the capsule and the anterior hyaloid face of the vitreous. Two of these nine eyes were lost—one through an endophthalmitis attributed to an operative complication, and the second from a late developing epithelial-endothelial dystrophy. The latter is a rare postoperative complication in cataracts and would not be expected in a 49-year-old man. The incidence of 60 percent broken capsules and 25 percent disastrous operative and postoperative complications suggests that eyes with cyclotron cataracts are not especially good subjects for operation.

Comment

Neutrons owe their cataractogenic action to the heavily ionizing irradiation which they produce in tissue. Since all types of ionizing irradiation produce the same qualitative tissue reaction, it is not surprising that the clinical symptomatology, the latent period and the threshold dose (allowing for the relative biologic effectiveness of fast neutrons and ordinary X rays) should be approximately the same in both cyclotron and X-ray cataracts.

Morphologically, in both instances, the initial changes take place in the posterior cortex and consist of fine dots and vacuoles. The dots may remain stationary or may slowly increase in size and density and form a mushroom or doughnutlike opacity between the posterior capsule and the nucleus. The anterior cortex is later affected and the nucleus is spared. The golden hue noticed in

a large percentage of the fast neutron cataracts has also been noted in the X-ray cataracts. The bluish tint occasionally noted by Sinskey[6] in radiation cataracts was not noted in any of the 13 patients here reported. Possibly these bluish opacities may have been of the cerulean variety and unrelated to the radiation.

The latent period between exposure and the development of lens changes in X-ray cataracts is generally given as from one to two years but may be as long as eight to 12. In the 13 cases here reported, it varied from a minimum of one year to a maximum of possibly six, or even longer. The average for the 13 cases was 3.5 years as closely as can be figured.

As concerns the threshold dose for the production of minimal lens opacities the relative biologic effectiveness of fast neutrons and X rays must be considered. In his recent review Ham[7] estimates that in terms of biologic effectiveness, dose for dose, fast neutrons are about five times more effective than 250 KVP X rays. He estimates the threshold cataractogenic dose of fast neutrons to be between 70 and 100 rads, and of ordinary X rays to be 400 to 500 rads. This figure is surprisingly close to the gamma equivalents calculated by Hunt in 1947 and Cogan in 1950.

In relation to the minimum threshold dose, patient No. 7 in this series is especially interesting. This patient was injured in a critical assembly accident in 1946. The exposure was on the left side, involving especially the head. Following the accident, there was epilation of the left side of the head, but not of the right. Three years later, the left eye developed cataractous changes which progressed for five or six years and thereafter remained stationary, reducing vision in the left eye to 20/40. The right eye developed minimal changes about two years later. These did not progress and did not interfere with vision. The dose received by the right eye must therefore have been close to the threshold dose which would produce minimal nonprogressive lens opacities in a 34-year-old man. Unfortunately, it is impossible to assign any definite neutron dose to this patient. The earlier estimate of 45 rad, made in 1953 by Dr. Ham, is now known to be based on incorrect dosimetry, and is regarded by Dr. Ham himself as totally invalid.

Patient No. 2 is also of especial interest. This patient received a single exposure of 120 rad to the head in December, 1943, and an undetermined but small amount thereafter. Visual failure was first noticed after a latent period of 130 weeks. The visual failure thereafter was extremely rapid. Nine months after the first symptom of visual failure, the left eye required operation and the right vision was reduced to 20/200. Thus a dose 50 percent above what is considered the minimal threshold dose did not shorten the latent period, but once cataractous changes began, they progressed with great rapidity.

The relation of the amount of fast neutron exposure to the latent period and to the rapidity of development of cataractous changes is subject to the error that the figures available for the amount of exposure are only an approximation, and definite conclusions cannot be drawn from them. This is reflected in the wide variations in the latent period and the differences in rapidity of the development of the cataracts shown by the individual patients to nearly the same estimated dosages. Nevertheless, when one groups these patients on the basis of the severity of the lens changes, and calculates the average latent periods and rapidity of development in the different groups, the results are interesting.

The Oak Ridge group[8] recognizes four general grades of severity in experimental radiation cataracts. Comparable groups in these 13 clinical cases would be: Group I, minimal changes with vision unaffected; Group II, slight lens changes which reduce vision to the 20/30 level; Group III, moderate lens changes which reduce vision to

the 20/40 or lower level; Group IV, severe lens changes which make cataract extraction necessary. The number of eyes in these four groups would be respectively 10, 3, 4, and 9.

The estimated average neutron dose received by the patients in these four groups, the average duration of the exposure, the average latent period between exposure and the development of incipient lens opacities, and the average rapidity of progression of the cataracts, are shown in Table 2.

In Group I the neutron dose was very slight, the duration of exposure 2.5 years, the latent period was 4.5 years, and no progression of the cataracts was observed after their first discovery.

In Group II the same figures are possibly 40 rads, four years, and the cataracts progressed slowly for two years, and thereafter remained stationary.

In Group III, the exposure was 40 rads, the average duration of exposure between one and two years, the latent period was three years. In three instances the lens opacities progressed steadily for two years and thereafter were stationary, while in one instance they progressed slowly over the eight-year period of observation.

In Group IV, the average exposure was 80 rads, the duration of exposure 42 weeks, the latent period about 10 months. In all cases except one the progression was rapid, the eyes being ready for operation within the first year.

If these figures are worth anything, they clearly indicate that the severity of the lens damage and the progression of the cataracts are in direct ratio to the neutron dosage received, while the latent period between exposure and the development of lens changes is in inverse ratio. In other words, the greater the dose of neutrons, the shorter the latent period, the more severe the lens damage, and the more rapid the progression of the cataracts.

The information available on these patients gives little indication of the relation of the duration of exposure to the cataractogenic action of fast neutrons. Experimental studies by Evans[9] indicate that chronic exposure to neutrons is highly cataractogenic. Cogan[10] found that the lens was apparently more sensitive to repeated small doses of X rays than was the skin. In this series of 13 patients the longest periods of repeated exposure were over 250 weeks (estimated total of 30 to 40 rad) in a Group III patient, and 250 weeks (estimated total 40 to 60 rad) and 200 weeks (estimated total 135 rad) in two Group IV patients. The shortest period of repeated exposure was 10 weeks (estimated total 30 to 100 rad) in a Group I patient. The duration of exposure in the other patients was in general from 25 to 40 weeks. The duration of exposure in the four groups varied from acute exposure to exposure over a five-year period. The wide variations in total estimated dosage and the uncertainty of the actual periods of exposure make it practically impossible to draw any definite conclusions on the relation of duration of repeated exposure to the cataractogenic effect.

It is generally believed that the young and actively growing lens is more sensitive to radiation damage than the older or mature lens. The age data on these patients give no information on this point The oldest patient in this group was No. 1, aged 47 years. This patient was estimated to have received 30 to 100 rads over a 30-week period and showed maximum damage (Group IV). The youngest was No. 4, aged 21 years at the time of exposure, received 80 rads over 25 weeks, and likewise showed maximum lens damage (Group IV). The average age of the four groups, from minimum to maximum lens changes, was respectively 29 years, 33 years, 33 years, and 31 years.

The results of operation in these patients suggested that eyes with cyclotron cataracts might be poor operative risks. The number of eyes operated upon is so small that no worthwhile conclusion on this point can be drawn. One might speculate that the ex-

posure to neutron radiation affected the nutrition of the eye adversely, but there is no supporting evidence for such a supposition.

The only pathologic study on these cyclotron cataracts is the one reported by Cogan, Donaldson, and Reese[11] on one lens. This showed a fibrillar thickening of the posterior capsule. Schlaegel[12] also noted a thickening of the capsule in victims dying of radiation sickness after the atomic bomb explosions, although it is not clear if this was analogous to that reported by Cogan, Donaldson, and Reese.

It is interesting that in two extractions of these cyclotron cataracts, the operating surgeon noticed an undue adhesion between the posterior capsule and the hyaloid face of the vitreous, a development which would make an intracapsular extraction more difficult. Cogan, et al.,[13] believed the posterior capsule was regularly involved in ordinary X-radiation cataracts. While it was specifically noted that the posterior capusle was not involved in the early stages of development of these cyclotron cataracts, it is quite possible it was involved in the later stages when the opacities had increased to the point that the opaque cortex was in contact with the posterior capsule.

The studies of Cogan, Donaldson, and Reese[11] indicate that the initial damage to the lens in ordinary radiation cataracts is to the epithelium at the equator. Here these cells piled up and it was hypothesized that they then made abortive attempts at formation of lens fibers. Unsuccessful in this effort, they were exfoliated off into the cortex and migrated toward the posterior pole where they underwent various degenerative changes, and ultimately were responsible for the posterior cortical opacities. Since the equatorial portions of the lenses could not be visualized clinically in these patients, there is nothing in the observations on them which throws any light on this point. The fact that in these cyclotron cataracts the early changes were definitely in the posterior cortex, and not in the capsule, is in favor of the above pathogenesis suggested by Cogan, Donaldson, and Reese.

Conclusions

An analysis of the clinical records of 13 physicists exposed to cyclotron irradiation between 1943 and 1946, who received repeated ophthalmologic examinations between 1949 and 1957, permits the following conclusions:

1. The cataracts in these patients were identical with the usual irradiation cataracts occurring after exposure to gamma rays, or X rays, both in their morphology and in the latent period between exposure and the development of the incipient lens opacities.

2. Although the estimates of dose given by these patients are little more than educated guesses, they indicate that about 80 rads of fast neutrons is a cataractogenic dose producing visual impairment.

3. The greater the amount of cyclotron irradiation received, the shorter appears to be the latent period, the more intense the lens damage, and the more rapid the progression of the opacities.

4. The information derived from these records is insufficient to warrant any conclusions on the relation of duration of exposure to the cataractogenic effect of the irradiation, or to the susceptibility of the juvenile lens as compared to the adult lens.

5. There is suggestive, but far from conclusive, evidence that cyclotron cataracts may be slightly poorer operative risks than ordinary senile cataracts.

6. There is nothing in these records which throws any light on the pathogenesis or mode of development of these cyclotron cataracts.

The Johns Hopkins Hospital (5).

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EXTERNAL OPHTHALMOPLEGIA*

As part of congenital myasthenia in siblings: Myasthenia gravis in children

Report of a family showing congenital myasthenia

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The diagnosis of myasthenia gravis is now made more frequently than when Levethan, Fried, and Madonick,[1] in 1941, reported finding only 34 cases in children less than 17 years of age (eight of these children were under 10 years of age). In 1956, Teng and Osserman[2] found that of 180 patients diagnosed as suffering from myasthenia gravis at the Mount Sinai Hospital, New York City, 21 were children (11.2 percent). Other reports of myasthenia gravis in infants and young children have appeared in the neurologic and pediatric literature in recent years, and one of us has reported one such case (Walsh, 1943, 1957).[3] It has become apparent that myasthenia in infants and young children does not constitute a single entity. In this paper we are concerned with the disease in this age group, and, since our cases closely resemble those of Levin's, we have included a summary of his case reports.

In 1949, Levin[4] proposed that the disease in this age group be divided into a number of clinically distinct groups. He discussed what he called neonatal myasthenia. This is a disease limited to newborn infants of mothers who themselves have myasthenia gravis. These infants often have a weak cry at birth, have poor respiration, and fatigue rapidly during feedings. The myasthenia is transient. Probably it is due to a circulating

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curarelike substance in the blood (which causes a block at the myoneural junction) obtained from the maternal placental circulation. Response to Prostigmin may be life saving. When the baby has replaced the mother's blood with its own it no longer has myasthenia gravis and does not require treatment. The affection does not redevelop. Strickroot, Schaeffer, and Bergo[5] reported the first instance of this type of myasthenia gravis in 1942. Ford,[6] in 1944, noted such a case. La Branche and Jefferson[7] reported it in 1949. Involvement of the eye muscles was noted only by Ford. Ptosis in some such cases was absent. We have notes on two such infants.

A second group mentioned by Levin is the familial form of myasthenia gravis. Onset may be at any age during childhood. There is a familial history of myasthenia gravis and the disease in the child represents more closely the classical form. Rothbart (1937),[8] Riley and Frocht (1943),[9] and Hart (1927)[10] described such cases.

Acquired myasthenia gravis also appears in young children without familial history of the disease. Such cases were the subjects of reports by Kawaichi and Ito,[11] Ford,[6] and Keynes.[12] Remak,[13] in 1892, described a condition which may well have been this disease. Levin considers this group as ordinary acquired myasthenia gravis with onset at an early age. Costenbader[14] recently has described three such cases.

Congenital myasthenia is a term used by Levin to describe a form of myasthenia which begins at birth (or before), is characterized by a mild onset, marked external ophthalmoplegia, partial ptosis, and symmetrical weakness of involved muscle groups. It may be associated with marked weakness of skeletal muscle especially of the neck, trunk, and leg muscles. In contrast to the usual form of myasthenia gravis it is not progressive, does not have remissions, and in the cases observed may improve with time. Response to Prostigmin is dramatic. It occurs in siblings without involvement of the parents and is variable in severity. Levin feels that this disease is not the myasthenia gravis described by Erb and Goldflam, though the basic defect (dysfunction at the myoneural junction) is the same or at least is similar. He concludes that myasthenia is a symptom complex resembling curarization and that it arises under a variety of circumstances.

Our cases which closely resemble those described by Levin probably belong to the group properly described as exemplifying congenital myasthenia. It seems possible that two cases (cousins) reported by Bowman[15] in 1948 belong in this group. Also a case report of Walton, Geschwund, and Simpson[16] could be included. They reported on an adult woman who was weak from birth and exhibited limitation of ocular movements; there was improvement when Prostigmin was administered but there was no response to Tensilon; they considered their patient to exemplify a borderland state between a dystrophy and myasthenia gravis and they used the eponym "benign congenital myopathy." In any event the cases here reported are observed rarely.

Summary of Levin's cases

A brother and sister showed the defect. There were no other siblings. The mother herself was completely normal. She reported that two of her first cousins had had ptosis (one cousin had marked ptosis). These relatives could not be found for examination. The father was normal and his family had not exhibited defects in muscles.

Case 1

Before the birth of this male infant the mother noted infrequent and weak quickening. Following birth the infant became cyanotic which was attributed to swallowing his tongue. Feeding was a problem and at times he would take only two or three ounces of milk. He sat at 10 months and walked at 17 months. When four years of age, bilateral partial ptosis was noted; the extraocular movements were severely limited especially for upward gaze and convergence; he had a drooping jaw and generalized hypotonia. On standing he had an exaggerated lumbar lordosis and he walked with a waddling gait. A diagnosis of nuclear apla-

sia (Moebius syndrome) was suggested. At six years of age his mother observed that he seemed better in the morning and weaker in the afternoon. Myasthenia was suggested as a possibility. Prostigmin was injected with dramatic results. His ocular movements increased greatly and his ptosis disappeared. He was immediately stronger.

At 10 years of age the child developed pneumonia. Unfortunately Prostigmin was withheld and death resulted.

CASE 2

The sister of this boy was three years younger. Before her birth the mother noted diminished or weak quickening. Her cry was weak at birth but she was not a feeding problem. She walked at 11 months but was unable to run until she was three years of age. At six months of age her mother noted that her lids drooped more at the end of the day although she was not sleepy. At the age of one year bilateral partial ptosis was obvious. The ocular movements could not be evaluated. She seldom fell after the age of seven years. At eight years of age her ptosis was minimal but her gaze movements though comitant were severely restricted. She could not look upward. Other ocular motions were about 30-percent normal. No other muscular weakness was found. Prostigmin injection produced marked retraction of her lids and she complained her eyes were "too big." Her ocular movements were markedly improved. The child did not tolerate Prostigmin orally because of abdominal cramps. Her medication was discontinued. She did well without benefit of the drug.

CASE REPORT (Walsh and Hoyt)

A family of six children recently studied at the Wilmer Institute presented unusual clinical findings. They were seen through the courtesy of Dr. Arthur B. King.

Although the parents and the two small daughters were completely normal all of the sons (four) had almost total external ophthalmoplegia and ptosis. The oldest son in addition had severe weakness of his skeletal musculature and was confined to a wheel chair. He was admitted to the hospital for study.

HISTORY OF THE OLDEST SON (P. Y., AGED 18 YEARS) (785106)

This boy had been a full-term normal infant. The mother reported a normal pregnancy and recalled that the infant was active in utero. Development seemed normal during the first few months. At the age of one and a half years he had a choking spell and was said to have had an enlarged thymus for which he received "light therapy." His mother noted drooping of his eyelids and inability to open the eyes fully. He was not a feeding problem. He attempted to stand at the age of one year. At this time the mother also noted generalized weakness. This weakness became more apparent during the next year. The boy walked poorly and he never ran. He preferred to sit. Often he would have to be carried into the house because he refused to walk. He contracted frequent and persistent chest colds associated with upper respiratory infections and was hospitalized on a number of occasions for pneumonia.

At four years of age because of his muscular weakness he was admitted to a childrens hospital for diagnosis and study. An almost total external ophthalmoplegia and partial bilateral ptosis were associated with rapid fatigability of his neck, trunk, and leg muscles. Extreme hypotonia was evident on this examination for the child could bend in all directions like a contortionist. He stood with marked lumbar lordosis. When he attempted to stand he did this in the manner typical of a muscular dystrophy (for example, he rolled first onto his stomach, then he pushed himself onto his feet and "climbed up" his legs to an erect position). Prostigmin was given intramuscularly at this time and a marked increase in muscle strength was obtained. A diagnosis, according to the mother, of muscular dystrophy with a "touch of myasthenia gravis" was made.

From the age of four years he took Prostigmin almost every day and at the time of our examina-

Fig. 1 (Walsh and Hoyt). *Congenital myasthenia.* Four boys in one family, all with ptosis and external ophthalmoplegia. The third boy from left also exhibited generalized muscular weakness.

Fig. 2 (Walsh and Hoyt). *Congenital myasthenia.* The same four boys as in Figure 1, following Prostigmin injection. Note improvement in ptosis. The oldest boy (right) is now able to stand.

tion was using one-half tablet every three hours. He had been able to walk for many years but at the time of examination he was confined to a wheel chair. Whether this resulted from advance of the disease or increase in weight is conjectural. He did well in school in spite of his disability and when seen at the Wilmer Institute (1957) he was about to enter college (age, 18 years).

He had no visual complaints except that he had been myopic for years.

Occasionally his voice became somewhat "weak" and his jaw tired with chewing.

Physical examination. He was normal in size and development for his age. He wore a myopic correction and had a partial bilateral ptosis which forced him to tip his head back to see. When fatigued, he would support his chin on his hands while sitting in his wheel chair.

He had marked generalized muscular weakness and could stand only with difficulty. He could walk only a few steps. He had a marked lumbar lordosis, slight winging of the scapulae, and a slight increase in the arches of his feet. There was slight wasting of the triceps, quadriceps, hamstrings, glutei, and gastrocnemei, and very slight wasting of the sternomastoids, deltoids, and pectoral muscles. The flexors of the neck were slightly weak. The elevators of the arms and flexors of the thighs were very weak. The remaining muscles of the extremities were moderately weak. His voice fatigued slightly. His vital capacity was good. His joints were hyperextensible. The tendon reflexes were normal and brisk, somewhat more active in his lower extremities. No pathologic reflexes were present. Blood pressure was 130/70 mm. Hg. The remainder of the examination was not remarkable except for the eye findings.

Ocular examination. The boy was myopic (−5.4D. in both eyes) and was correctible to 20/20 in both eyes. There was bilateral partial ptosis and extreme limitation of motion of both eyes. An alternating esotropia of approximately 20 prism diopters was present. Pupillary reactions to light and accommodation were normal. The only ocular motions present were infraduction (10 degrees) and adduction (10 degrees) in both eyes. Convergence was nil. Color vision was normal. The fundi revealed mild myopic changes. Slitlamp examination gave normal findings. On sustained attempted upward gaze his lids fatigued rapidly and his ptosis increased. Lid closure, however, was powerful.

Prostigmin test. First the boy was asked to stand and he could do so only with assistance. After a few steps he almost collapsed to the floor. He attempted to get up from the floor from a prone position and was almost unable to do so, arising to a standing position by "climbing up his legs."

Prostigmin methylsulfate (1.5 mg.) was injected intramuscularly, preceded by 0.6 mg. of atropine sulfate. Following injection of the drug no ill effects were experienced and there was absence of muscular fibrillations. Thirty minutes after injection he was re-examined. Response to the drug was dramatic. He could arise promptly from a prone position without using his hands. His ptosis and neck weakness disappeared and his ocular motions with the exception of upward gaze returned to approximately 70 percent of normal.

Special examinations. Laboratory examinations gave normal findings. NPN = 31 mg. percent; creatinine 0.9 mg. percent; glucose tolerance was normal; blood sugar 124 mg. percent; Na +139.0

MEQ/L, K+ 4.4. MEQ/L. cholesterol 240 mg. percent; serum protein 8.1 gm. percent (albumin 4.5 gms. percent; globulin 3.6 gms. percent). Serology, negative. Blood count, normal. Chest X-ray films were not remarkable.

Electromyography of the skeletal musculature showed classic fatiguing of muscle with "fall-out" of action potentials. Response to Tensilon was classic for myasthenia with immediate increase of action potential spikes and sustained nonfatiguing of muscle (examination by Dr. David Grob).

Electromyography of the ocular muscles was done. Tracings taken from the lateral rectus showed rapid fall-out of motor units with sustained contraction and low amplitude of action potentials. After Tensilon the amplitude was immediately greater and frequency of motor discharge was normal without evidence of fatiguing with sustained contraction. This record was typical of myasthenia in ocular muscles as reported by Breinin[17] in 1957.

Muscle biopsy was made of the gastrocnemius muscle and was reported as normal without evidence of muscular dystrophy.

Examination of other siblings

1. *M. Y., aged 16 years.* This boy had marked ptosis and almost total inability to move his eyes, first recognized at one year of age. Ocular movements were limited to two to three degrees of infraduction and two to three degrees of adduction in each eye. He had never taken part in running games though he could walk long distances. He complained of thickening of his speech toward the end of the day. Physical examination revealed no muscular wasting. He had slight weakness of his orbicularis oculi plus slight weakness of the muscles of his neck, shoulders, and of the pelvic girdle.

The Prostigmin test yielded a positive response. He had actual lid retraction and his ocular motions improved slightly. Electromyography of his ocular muscles revealed rapid fatiguing and immediate return of strength with injection of Tensilon. There were no fibrillations.

2. *S. Y., aged 10 years,* had ptosis similar to his brothers and had only two degrees of infraduction of both eyes. He was reported to run with a peculiar swinging gait and to have some weakness when chewing. He was a well-developed normal boy with moderate weakness of his neck muscles and slight weakness of his girdle muscles.

The Prostigmin test showed a marked response with regards to his neck weakness and his ptosis. His extraocular movements were only slightly improved.

3. *M. Y., aged eight years,* was the youngest brother. He had a total external ophthalmoplegia since birth with ptosis. He apparently suffered from no other mucular weakness but he could not run as fast as his younger sisters. Physical examination revealed moderate weakness of the orbicularis oculi, frontalis, and slight weakness of the flexors of his neck and thighs.

In the Prostigmin test the response was positive. His ptosis improved as did the strength in his neck and thighs. His ocular motions were little improved.

Differential diagnosis and Discussion

This family group of four boys presents an interesting problem in diagnosis both for the ophthalmologist and the neurologist. They exhibited almost total bilateral external ophthalmoplegia with partial ptosis which almost certainly was present from birth. If the younger members of this family had been examined without knowledge of the older boy with generalized muscular problems they might have been diagnosed and reported as congenital (sex-linked?) external ophthalmoplegia. Such reports in the literature are not uncommon.

In 1950, Salleras and Ortiz de Zarate[18] reported on a group of such cases with myopia. Ibraham,[19] in 1955, reported two cases in brothers associated with slight mental retardation. Holmes,[20] in 1956, reported on hereditary congenital ophthalmoplegia. It must not be implied that these reported cases all represent the same disease entity as our cases, for certainly there are a number of causes for congenital ophthalmoplegia. Mention of the use of Prostigmin has not been included in reports of such cases and it seems likely that among them some might have responded to the drug as did our patients.

Though it had been suspected previously, it was Kiloh and Nevin[21] (1951) who established progressive nuclear external ophthalmoplegia as a muscle disease rather than a nuclear dysplasia. Under the title, "Progressive dystrophy of ocular muscles," they did not mention the association of myasthenia with the ocular muscle involvement in small children but they did point out the occasional association of external ophthalmoplegia with muscular dystrophy. Walton and Nattrass[22] mentioned external ophthalmoplegia with myotonia congenita. Schwarz and Chan-Nao Liu,[23] in 1954, reported again the pathologic changes in the ocular muscles and described it as a dystrophy.

This family just reported showed characteristics of muscular dystrophy occurring in males (weakness and lordotic posture of the 18-year-old boy).

Amyotonia is to be considered. The profound atonia and areflexia of this disease were not present. Normal tendon reflexes, the lack of muscular wasting, and especially the marked fatigability of the muscles which are unusual for muscular dystrophy are characteristic for myasthenia gravis.

Batten[24] (1910) referred to a small group of patients who presented a transitional stage or clinical picture between muscular dystrophy and muscular fatigability seen in myasthenia gravis. Recently Walton and Nattrass reviewed the myopathies and mentioned a case they had seen of muscular dystrophy with marked fatigability and a positive response to Prostigmin which "invited a diagnosis of myasthenia gravis."

Levin's cases and those reported here are not clearly examples of myasthenia gravis (if they are, they are an atypical form) or of muscular dystrophy. Elements of both are present. Levin's term "congenital myasthenia" probably is the most satisfactory.

With regard to the hereditary transmission little can be said. Probably our cases were the result of a mutation in that more than one case occurred in a family without previous family history of such a disease. Levin's cases were brother and sister (two cousins were also involved). In the cases reported here only male siblings were affected suggesting a sex-linked recessive inheritance.

If cases of congenital external ophthalmoplegia are examined with regard to response to Prostigmin and with electromyography of the ocular muscles more such cases may be uncovered.

Summary

1. The various types of myasthenia in children are discussed and the characteristics of congenital myasthenia are defined.

2. Four cases of congenital myasthenia with external ophthalmoplegia occurring in the male children of one family are described.

3. Partial ptosis and almost total external ophthalmoplegia was the outstanding finding.

4. One member of this family had severe generalized weakness and fatigability of his skeletal musculature which was symmetrical and which showed neither remissions nor improvement with time. Response to Prostigmin was dramatic.

5. The use of Prostigmin and electromyography is urged in the differential diagnosis of congenital external ophthalmoplegia.

Addendum

We overlooked a paper by Macrae[25] written in 1954. He described four cases of myasthenia gravis in early childhood. He had one patient whose mother exhibited hyperthyroidism which is of interest in the light of an apparent relationship in adults.

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NEW IRRIGATING DEVICE ESPECIALLY USEFUL FOR ANTERIOR CHAMBER IRRIGATION*

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There are many situations in the practice of ophthalmology where it is desirable to have a sterile irrigating solution. The prime example is in irrigating the anterior chamber during cataract surgery. It is easily possible by anterior chamber irrigation to introduce micro-organisms, lint, and other particulate matter. Christensen and Swan† have noted particularly the deleterious effects of lint in the anterior chamber. Many solutions used in eye surgery may be sterile yet contain lint and other particulates. Other solutions thought to be sterile may be questionably so.

One simple answer to this extremely important problem is the integration into the irrigating system of a Millipore bacterial retentive filter membrane in a Swinny Filter Adaptor.‡ Figure 1 illustrates such an assembly. The millipore filter is a thin cellulosic membrane having approximately 50,000,000 capillary pores of uniform dimensions per square centimeter of filter surface. The pores are 0.4 ± 10 percent microns which thereby retain the smallest bacteria and naturally all inanimate particulates. The filter membrane is the basic component of a standard method for bacterial testing of water having been approved by the U. S. Public Health Service, the National Academy of Sciences, and other agencies and scientific associations, and is widely used in other types of bacterial counting studies.

The lower half of Figure 1 illustrates the assembly. The filter adapter is attached by

* From the Francis I. Proctor Foundation and The School of Pharmacy, University of California Medical Center.

† Christensen, L., and Swan, K. C.: Personal communication.

‡ The membrane filter and the Swinny adaptor are available from the Millipore Filter Corporation, Watertown, Massachusetts.

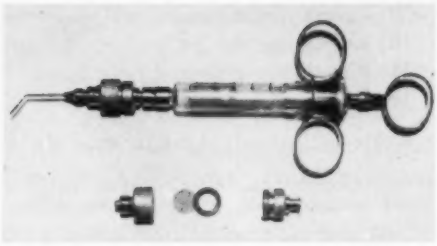

Fig. 1 (Vaughan and Riegelman). Swinny filter apparatus adapted for anterior chamber irrigation, showing assembled and dissembled parts.

a Luer-Lok to a standard glass or bulb syringe and irrigating needle. The filter apparatus is prepared for use by inserting the support screen, followed by the filter membrane and rubber washer. The two sections of the adapter are screwed together but not tightened. The combined apparatus is then wrapped and autoclaved. When the apparatus is to be used, the adapter is firmly tightened and temporarily removed from the syringe. The irrigating solution is then drawn into the glass syringe or the bulb and the Swinny adaptor and irrigating needle are then reattached.

Experience in using this assembly has proven that little pressure is required to force the fluid through the filter membrane.

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Medical Center (22).

THE SYNDROME OF THE AORTIC ARCH*

Ocular manifestations of "pulseless disease" and a report of a surgically treated case

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Introduction

The multiplicity of signs and symptoms which may be associated with an insufficiency of blood supply through the great vessels arising from the arch of the aorta has, until relatively recent years, received scant attention in medical literature in general, and in the American literature in particular. This lack of interest is even more apparent in relation to ophthalmology, if one is to judge by the paucity of information which is manifest in the various ophthalmic journals. The work of Currier, DeJong, and Bole[1] would indicate that the ocular manifestations of the condition represent its most common and constant symptomatology (32 out of 40 cases), and it would seem, therefore, that it is worthy of re-emphasis. If, as seems likely, the disease entity is more common than is generally supposed, it is even more incumbent upon the ophthalmologist to recognize his findings for what they are, since they may represent the only apparent evidence of the underlying disorder.

Historically, the first description of some of the sequelae of obstruction of the innominate and of the left common carotid and subclavian arteries was recorded by Davy[2] in 1839. His first patient was an English Army officer, and trauma, in the form of a perforating wound of the chest ostensibly sustained at the Battle of Waterloo, was prudently listed as the etiologic factor. However, the large aneurysmal dilatation of the thoracic aorta, which was noted at autopsy and which subsequently resulted in the difficulties which beset its owner, was more than likely luetic in origin. Another somewhat similar case was later reported by Davy, and, in 1875, Broadbent[3] published his observations on another patient with an absence of radial pulsations. Türk,[4] in 1901, recorded what we consider to be the first

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fairly complete description of the varied manifestations of obstruction of the branches of the aortic arch.

In 1908, Takayasu[8] first emphasized and adequately described the ocular manifestations of what was later to be called the "aortic arch syndrome." In spite of the fact that the associated eye findings, however prominent they may be, represent only one facet of a far more widespread and much more lethal pathologic state, the entire disease complex has in recent years been referred to as "Takayasu's disease." While the employment of this nomenclature in the Japanese literature is quite understandable, its general use should be discouraged because of the limited scope of the original work and because of its implication of originality.

There is little doubt that the ophthalmologic portrait of this syndrome has as its foundation hypoxia of ocular tissue. This hypoxia is also manifest in other organs, such as the brain, which are dependent for their nourishment on the patency of the large vessels arising from the aortic arch. Occlusion of these vessels, whether partial or total, results in a somewhat constant and relatively characteristic disease, its severity depending upon the degree of such obstruction. The terminology applied thereto is somewhat less than constant, if one is to judge from the titles which are encountered in the literature. For example, the following all refer to the disorder under discussion, despite their varying emphasis on signs, symptoms, and etiology:

1. Takayasu's disease[8]
2. Aortic arch syndrome[6]
3. Pulseless disease
4. Chronic subclavian-carotid obstruction syndrome[7]
5. Ophthalmo-angiopathic hypotonica[8]
6. Thrombo-arteritis obliterans subclaviocarotica[9]
7. Obliterative brachiocephalic arteritis[10]
8. Martorell's syndrome[11]
9. Reversed coarctation[12]
10. Anisosphygmia
11. Pulsus incongruens
12. Pulsus differens

It is obvious that the last three of the several basically synonymous disorders, listed above, refer to the symptomatology of only one of the many dysfunctions which are attributable to circulatory insufficiency in the upper extremities. These are, therefore, poor terms to employ in reference to the entire disease entity. "Reversed coarctation," a coinage based upon the frequent presence of hypertension in the lower extremities existing concurrently with absent pulse pressure in the upper limbs, is admittedly unacceptable even to its authors. "Pulseless disease" is as vague and nonspecific a title as "pulsus incongruens." Further, any use of the "itis" suffix is semantically improper in view of the lack of concrete evidence that a true inflammatory process is the etiologic factor. Although there is a great temptation to enrich the medical literature by adding one more name to an already ample and constantly burgeoning list, we feel that, at least in the light of our present knowledge of the subject, the term "aortic arch syndrome" is adequate and sufficient.

Much of the confusion which exists relative to the nomenclature of the syndrome is based upon a lack of proper definition. The term "pulseless disease" seems inappropriate and misleading because it implies total absence of pulsation in the neck and arms. The excellent reviews of Ross and McKusick[13] (100 cases), and Currier, et al.[1] (40 cases), include, under the term "aortic arch syndrome," cases of incomplete occlusion in which all pulsation was not absent.

A second point of confusion has arisen out of attempts to delimit further the syndrome from the standpoint of etiology; in other words, to restrict it so as to include only those cases in which there is no demonstrable evidence of any other specific and

commonly recognized disease entity. This view of the matter is well expressed by Kinney[14] in reporting a case of "pulseless disease." She states in part:

> It may be caused by syphilitic arteritis and, somewhat less commonly, by syphilitic aneurysm. It occurs rarely in dissecting aneurysm and in traumatic injuries of the thorax. When these conditions have been excluded, there remains, as reported from the United States, Great Britain, the Scandinavian countries, and Japan, a group of patients in whom the etiology is unknown. The name, pulseless disease, has been designated for this group.

There are good reasons, however, why etiology should not be considered when one places a given set of findings into the category of the aortic arch syndrome. First of all, there are the obvious diagnostic problems; in Currier's case,[1] there was a positive Treponema immobilization test in the absence of positive blood and spinal fluid serology, suggesting that the latter laboratory findings are inadequate to rule out the diagnosis of luetic aortitis. Conversely, the unquestioned diagnosis of systemic syphilis should not lead us to the fallacious conclusion that there is no other concurrent disease process which might account for the presenting symptoms. An adequate diagnosis from the pathologic standpoint is particularly difficult in view of the relatively few cases which have been autopsied; according to Bustamante[7] and his co-workers, only seven postmortem studies were available prior to their report in 1954.

There is no doubt that further progress in medical research will uncover more and more factors related to the causation of the occlusion of the great vessels involved in this disorder. We feel, therefore, that the aortic arch syndrome should be inclusive of all clinically similar disorders which meet the necessary criteria irrespective of their etiology.

Incidence

Of the cases which have been reported up to this time, the majority have appeared in the Japanese literature. Out of 89 cases reviewed by Chang[15] and his co-workers in 1955, approximately two thirds were Japanese. These figures correlate with those of Ask-Upmark,[16] who, in 1954, was able to collect only 28 cases which had been observed outside of Japan. It is doubtful that the true incidence of the syndrome is higher among the Japanese. It is more probable that the work of Takayasu stimulated further investigation by his countrymen, prior to the spread of interest to other areas.

In the Japanese literature, the highest incidence is among women, particularly in the younger age group (20 to 30 years). Reports from other countries indicate no sharp dividing line on the basis of sex, and the age group averages 40 to 50 years. The limited state of our knowledge, however, does not permit any definite conclusions to be drawn from this apparent inconsistency.

The distinction of reporting the first cases belongs to Davy, Broadbent, and Türk. After Takayasu, the first case in a nonoriental was described by Harbitz and Raeder[17] (1926). The next case report was that of Cohen and Davie[18] in 1933, in which there was complete obliteration of the orifices of the three great vessels in association with a syphilitic aortic aneurysm.

The first American case was that reported by Caccamise and Whitman[19] in 1952, the authors claiming it to be, incorrectly, the first outside of Japan. In 1954, Caccamise and Okuda[20] presented the first case report to appear in the American ophthalmic literature.

The relatively recent awakening of interest in the aortic arch syndrome, particularly on the part of American and English investigators, may well alter many concepts relating to its incidence. The rapidly increasing number of case reports may soon show that it has no particular predilection for females, that its age distribution is extremely wide, and that orientals are affected no more frequently than any other race. It is already becoming apparent that it is, by no

means, as rare a condition as was once thought.

Generalized signs and symptoms

As previously stated, the entire complex of signs and symptoms which are present in the aortic arch syndrome has, as its basis, occlusion of the innominate and the left subclavian and common carotid arteries, from whatever cause. This complex has been most completely documented by Martorell and Fabre,[11] first in 1944. The findings include:

1. Absent or diminished pulses in the neck and upper extremities
2. Weakness and paresthesia of upper extremities
3. Transient hemiplegia or monoplegia
4. Headache
5. Transient blindness in one or both eyes
6. Transient aphasia
7. Syncope
8. Hypertension in lower extremities
9. Trophic disturbances in head and neck, including the eyes
10. Occasional fever, leucocytosis and elevated sedimentation rate

It is of interest to note that, in spite of the complete absence of pulsation in the head and neck, there is little or no evidence of ischemia in the arms and hands. Obviously, this is due to the fortuitous development of normally adequate collateral circulation, which is maintained in spite of a total damping of the pulse wave. That such collateral channels are not completely sufficient is evidenced by the common, and frequently the presenting complaint of claudication and paresthesias in the upper extremities following exercise, particularly when the arms are raised (Jervell[21]). Similarly, intermittent claudication of the masticator muscles is a common finding.

All of the cerebral manifestations of the syndrome likewise stem from vascular insufficiency, indicating that the newly established collateral circulation barely meets the minimal nutritional requirements of the brain. It does not seem necessary to attribute the observed attacks of syncope to hypersensitivity of the carotid sinus. In addition to syncope, transient monoplegia, hemiplegia, and aphasia are not uncommonly noted. The headache, which is usually a very distressing symptom, is ordinarily dull and is temperofrontal in its distribution.

The onset of the disease is rather insidious, as is evidenced by the fact that symptoms appear only after the occlusive vascular phenomena are quite well advanced. Its duration has been reported by Chang[15] to be 1.5 to 14 years. Currier, DeJong, and Bole[1] list the average duration as 3.2 years, stating that if it is shorter, death occurs due to cerebral ischemia. If the duration is longer, sufficient collateral circulation has developed so that death can be ascribed to some other cause, such as rupture of an aneurysm.

Ocular manifestations

The visual symptomatology of the disease follows as a consequence of the greatly altered blood supply to the head. Transient blurring or complete loss of vision in one eye is a frequent symptom of unilateral carotid insufficiency or thrombosis. Since both common carotid arteries are occluded in the aortic arch syndrome, it does not seem peculiar that these patients experience transient loss of vision in one or both eyes, and that such loss may be either partial or complete. Frövig[6] reported such instances occurring only while the subject was engaged in physical activity and hence referred to the symptom as "visual claudication." Shimizu and Sano[9] recorded the precipitation of such attacks following changes in posture, or extension of the neck. Increased susceptibility to attacks of transient amaurosis have been noted in male patients wearing tight collars, which impeded the collateral channels running superficially. All this is considered to be the direct result of retinal ischemia in consequence of fluctuations

in the already embarrassed blood supply to the head, and is symptomatically identical to the "amaurosis fugax" which is so frequently referred to in ophthalmic literature.

The lack of an adequate retinal blood supply is evident on objective grounds as well. As was noted in the case which we are reporting, the pressure in the ophthalmic artery may be so low that the vessel can be occluded by only the slightest pressure on the globe. Hollenhorst[22] states that the retinal arterial pressure may be so low that it is practically immeasurable with the ophthalmodynamometer. It may be sufficiently low so that postural hypotension, resulting from a change from the reclining to the sitting position, will cause observable pulsation in the central retinal artery and segmentation of the blood column.

The numerous other observable changes in the ocular structures occur as a direct result of chronic hypoxia, and are for the most part irreversible. Ostler[23] has presented the most recent and complete listing of these eye signs in conjunction with a case report, and calls attention to the fact that early in the disease the fundus may appear normal or there may be merely a few microaneurysms in the periphery of the retina. Dilatation of the veins with beadlike swellings are next noted, and finally arteriovenous communications appear which encircle the optic disc. This latter condition was illustrated in the article by Shimizu and Sano,[9] and the term "anastomosis peripapillaris progressiva" was applied to it by Caccamise and Okuda.[20] Similar arteriovenous anastomoses were described by Leo[24] as occurring in the conjunctiva, and Skipper and Flint[25] have called attention to the appearance of newly formed vessels running circumferentially at the root of the iris.

Leo[24] also noted the presence of internal ophthalmoplegia, presumably on the basis of the chronic ischemia of the ciliary body and iris. The reduced blood flow to the ciliary body is also undoubtedly responsible for the greatly lowered intraocular pressure which commonly occurs as part of the syndrome. Late complications, occurring when the disease is well established, consist of cataract formation, optic atrophy, retinal detachment, retinitis proliferans, vitreous hemorrhage, and corneal opacification. Occasionally, cataract formation may occur early enough to obscure the vascular phenomena in the retina. Occasionally, too, as in the case reported by Gibbons and King,[10] there is no evidence of ocular involvement to any great degree, in spite of the presence of the other characteristic findings.

Etiology and Pathology

If we include, within the circumference of the aortic arch syndrome, all possible causes of the vascular occlusion which produces it, syphilitic aortitis emerges as the most commonly suspected etiology. Ross and McKusick[13] have concluded that the secondary atheromatosis of a syphilitic aorta may be an important contributing factor, but that the presence of an aneurysm was not essential to the development of the disease. In Currier's[1] series, however, there were 12 cases with aneurysm as opposed to only four cases of luetic aortitis without aneurysm. Skipper and Flint,[25] reporting on 18 cases including two of their own, presumed a luetic etiology in exactly 50 percent. It is probable, however, that the importance of syphilis as a causative agent has been underemphasized; according to Morgan,[26] a positive Wassermann reaction is found in somewhat less than 80 percent of all cases of uncomplicated aortitis of luetic origin. He emphasizes the importance of spinal fluid examination, since this may yield a higher percentage of positive results.

Trauma is another etiologic factor which has sometimes been implicated. The first case reported by Davy[2] is a prime, although dubious, example. One of Ross and McKusick's patients had sustained chest trauma some 13 years prior to the onset of symptoms, which prompted their suggestion that such injuries may lead to eventual occlusion

of the branches of the aorta.

Tuberculosis was incriminated by Shimizu and Sano[9] on histologic evidence, although they did not attempt antituberculosis therapy. Harbitz and Raeder[17] reported an inflammatory process of infectious character in the walls of the aorta, possibly of streptococcal origin. Generalized arteriosclerosis was suggested as the etiologic agent by Davis, Grove and Julian,[27] and in Lawson's[28] case there was a history of familial hypercholesterolemia. Perhaps the most unusual hypothesis as to the origin of the disease has been advanced by Trias de Bes[29] and his associates on the basis of the examination of an enucleated human eye; they infer that because of the many congenital mesenchymal abnormalities which they observed, the disorder is based upon some familial or hereditary predisposition.

Aside from luetic aortitis, either with or without aneurysm formation, the most commonly accepted causation of "pulseless disease" is a completely nonspecific type of arteritis which preferentially involves the aortic arch. This would, of course, be compatible with the not infrequent findings of leucocytosis, fever, and elevated sedimentation rate in conjunction with the other manifestations of the syndrome.

Frövig[6] first suggested its relationship to the group of diseases of "allergic-hypergic" origin, and this viewpoint has gradually come to be quite commonly accepted. Bustamante et al,[7] feel that the process falls in this category, and that it is therefore related to polyarteritis nodosa, temporal arteritis, endarteritis obliterans, and so forth. The histologic features of endangiitis obliterans were demonstrated in the resected portion of a thrombosed common carotid artery in the report of Mangold and Roth.[30]

The similarity of the pathologic picture in this disease to that observed in the so-called "collagen diseases" has also been noted by Chang.[15] Weir and Kyle,[12] and Skipper and Flint[25] also list nonspecific aortitis as the most likely etiologic agent. In the case observed by Bowling, Stephens and Dein,[31] the symptoms and signs referable to the aortic arch represented only one phase in the progression of an arteritis which eventually resulted in the occlusion of the iliac vessels. Histologic studies here showed angiitis along with focal necrosis of muscle tissue.

From the above, it is obvious that there is, and has been, considerable debate as to the etiology of the aortitis which has, as its consequence, the obstructive phenomena producing the aortic arch syndrome. Its dissimilarity to thromboangiitis obliterans (Buerger's disease) is manifest in the tendency for the latter to affect primarily medium-sized vessels. Periarteritis nodosa also has a predilection for medium-sized vessels, especially those of the viscera, and usually spares the larger ones, such as the aorta. It is doubtful that either tuberculosis or trauma can logically be implicated as a primary cause of "idiopathic" occlusion of the innominate, subclavian and carotid arteries. The choice of diagnosis, therefore, lies between syphilis (perhaps in the face of negative serologic studies) and an unusual form of arteritis which selectively affects the aortic arch and which produces a somewhat different microscopic picture than do the members of the collagen or "hypersensitivity" group of diseases.

Treatment

Logically, the treatment of the patient should be directed toward the primary pathologic process, assuming that it can be established. Antiluetic therapy is certainly indicated in those instances where a positive serology is present. It should be remembered, however, that once the picture of obstruction of the great vessels of the aortic arch presents itself, one can expect little or no improvement as a result of such treatment.

Gibbons and King[10] have reported on the subjective improvement which was noted by a patient treated with corticosteroids (prednisone 10 mg. every six hours) and suffi-

cient anticoagulants so that the prothrombin concentration was between 10 and 20 percent of normal. Since these drugs were administered simultaneously, it is difficult to assess their relative values. In addition, aside from the symptomatic benefit reported by the patient, no other improvement was observed.

The surgical approach to the disease has been, until quite recently, unsatisfactory. Cervical sympathectomy has been attempted, but is ineffective. The first report of a more definitive surgical procedure appeared in Ross and McKusick's[13] survey; one of their cases had a portion of lyophilized infant aorta grafted between the arch and the patent distal portion of the common carotid artery. There was apparent relief of symptoms, but no details as to the follow-up of this patient were given. Shimizu and Sano[9] grafted a portion of saphenous vein into an area of the resected thrombosed carotid artery; they also perfomed denervation of the carotid sinus. This apparently relieved the syncopal attacks, but there appeared to be little flow of blood to the brain through this reconstructed vessel. Davis, Grove and Julian,[27] in 1956, opened the innominate artery and curetted and irrigated a large amount of "thrombotic and sclerotic debris" from it. Recovery from the procedure was uneventful.

There is no doubt that the rapid advances in vascular surgery, made possible in large measure by the use of hypothermia, will soon permit the radical reconstruction of the aortic arch. In this connection, we believe that the following report of a surgically treated case of the aortic arch syndrome is of considerable interest.

Case report

The patient, a 50-year-old white woman, complained of transient attacks of blindness in one or both eyes, in association with mild headache and intermittent hemiplegia. The episodes of blindness began in 1955 and involved most often the left eye. Attacks occurred at approximate intervals of three weeks and lasted from five to 10 minutes. Most commonly, vision in the involved eye was completely absent, although on occasion there would be only blurring. The attacks were not heralded by "flashes of light" or other entoptic phenomena, nor were they related to activity, or to time of day. She experienced a dull, bitemporal headache during some of the attacks, and also noted three or four episodes of transient hemiplegia as well. On one occasion, she experienced aphasia lasting for three to four minutes.

Approximately three months prior to her admission to the Herbert C. Moffitt Hospital, University of California, the attacks became more frequent and could be precipitated by rising from a chair or getting out of bed quickly. She began to notice dizziness and giddiness along with the visual symptoms, although between episodes she felt completely well and was able to perform her work as a cook in a small restaurant. Just prior to her hospital admission, she experienced several "attacks" per day.

Past history was notable insofar as a diagnosis of syphilis had been made in 1936 and she had been treated for three years with "injections."

General physical examination revealed significant findings only in the eyes and in the cardiovascular system. With reference to the latter, neither radial nor carotid pulses were palpable bilaterally. The systolic blood pressure was recorded as: 40 mm. Hg, right arm; 60 mm. Hg, left arm; 140 mm. Hg, both legs. The heart was not enlarged and only a faint systolic murmur could be heard over the aortic area.

Neurologic examination was completely within normal limits and revealed no residua of the past episodes of hemiplegia.

Ocular examination showed anisocoria, the left pupil being larger than the right. Both pupils were fixed to light and accommodation. Extraocular movements were normal. The intraocular pressure was markedly reduced in both eyes (O.D., 6.0 mm. Hg; O.S., soft). Vision was 20/20 in each eye without correction and visual field examination (peripheral and central) was entirely normal. Amplitude of accommodation was nil. There were no lens changes.

Fundus examination revealed markedly dilated veins which, in some areas in the midperiphery, demonstrated peculiar segmentation. The arterioles were irregular in caliber with areas of localized narrowing, but no aneurysmal dilatations were seen and no peripapillary arteriovenous anastomoses were observed. There were no hemorrhages or exudates and the discs appeared normal. Pulse pressure in the retinal arterioles was almost nonexistent, and the arterial tree could be completely blanched by exerting minimal digital pressure upon the globe (fig. 1). Ophthalmodynamometric examination was: (*Diastolic*) O.D., 30; O.S., 29. (*Systolic*) O.D., 36; O.S., 32.

Laboratory findings including blood and spinal fluid analysis for syphilis were entirely negative.

Special studies included a retrograde femoral arteriogram which was done to visualize the aortic arch and its branches. Except for the first centi-

Fig. 1 (Tour and Hoyt). Photographs of the optic nervehead and central retinal vessels before (left) and after (right) slight digital pressure upon the globe. The resultant blanching of the vascular tree is evident. The photograph on the left also demonstrates the venous dilatation which occurs in the aortic arch syndrome.

meter of the innominate artery distal to its origin there was no filling of this vessel; there was likewise no filling of the proximal four or five cm. of both common carotid arteries, and the proximal one third of both subclavian arteries. There was delayed filling of the peripheral portions of the right carotid and the subclavian arteries, presumably by way of collateral channels (figs. 2, 3, and 4).

Electroencephalography showed no general abnormalities or focal changes.

Surgery was undertaken on July 14, 1958.* Under general anesthesia and hypothermia, the aortic arch was exposed through a vertical midsternal approach. Firm, localized obstructions could be palpated in the innominate, left carotid and left subclavian arteries (fig. 5). A thromboendarterectomy of the innominate and left common carotid was performed; at the conclusion of this a bounding pulse was present in the right brachial and in both carotid arteries (figs. 6, 7, 8, 9, and 10).

The patient's recovery was rapid following the operation and she was ambulatory in three days. Her complaints relative to transient visual loss did not recur.

Postoperative eye examination revealed that the arterial circulation could no longer be occluded with light pressure on the globe. On the day following surgery, the intraocular pressure was 15 mm. Hg in the right eye, and 10 mm. Hg in the left.

Ophthalmodynamometric readings were: (*Diastolic*) O.D., 65; O.S., 60. (*Systolic*) O.D., 105; O.S., 80. Two months later, the following readings were obtained: (*Diastolic*) O.D., 70; O.S., 60. (*Systolic*) O.D., 100; O.S., 96.

Pathologic examination of the material removed from the innominate artery showed the presence of a large organizing thrombus surrounded by a thin layer of intima, which had undergone hyalinization and arteriosclerotic change.

Discussion

Although the actual pathologic alteration in this case was located at the level of the aortic arch, the most troublesome symptoms reported by the patient were visual. Collateral circulation to the head must have been adequate to meet the demands of the central

* We are indebted to Dr. Edwin J. Wylie of the Department of Surgery, University of California School of Medicine, who performed the operation, for his generous co-operation and helpful suggestions. We also wish to thank Miss Diane Beeston and Miss Joan Esperson for their invaluable assistance in the matter of photography and art work.

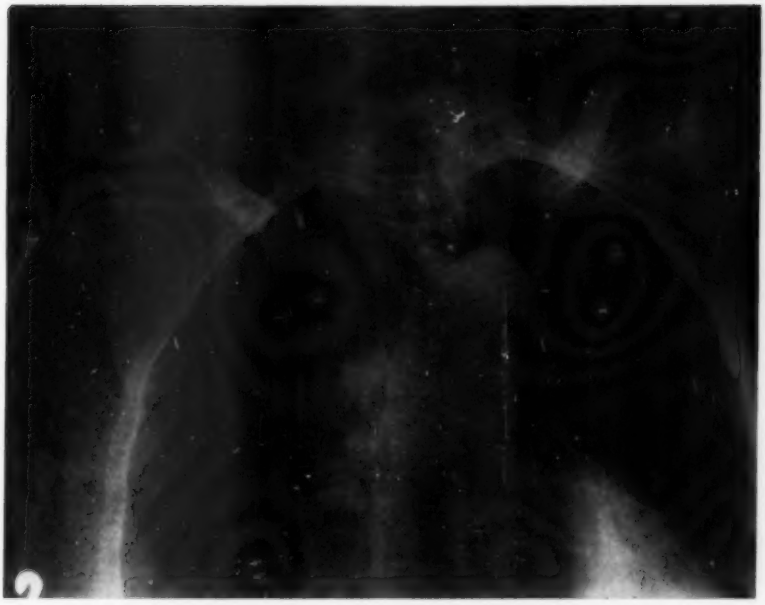

Fig. 2 (Tour and Hoyt). Radiographic study of the aortic arch immediately following femoral injection of contrast medium. There is filling of only short portions of each of the great vessels involved. (Initial phase aortagram.)

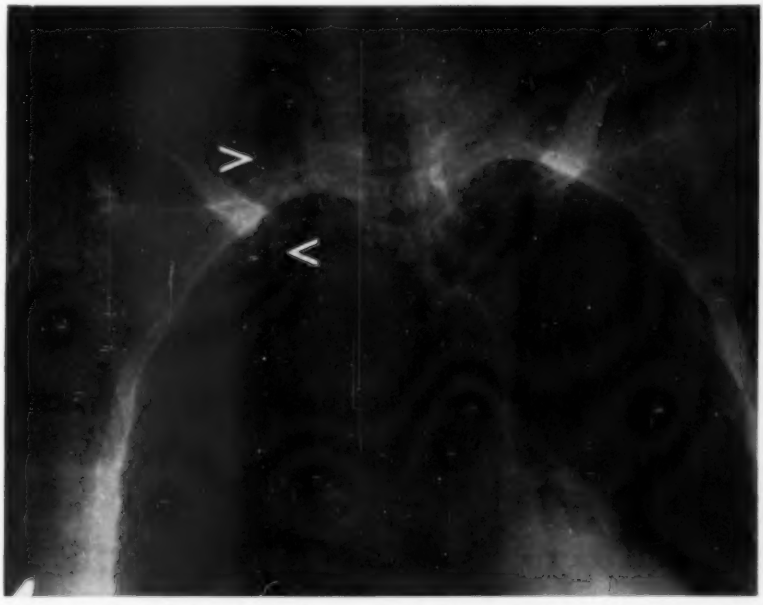

Fig. 3 (Tour and Hoyt). Intermediate phase aortagram, demonstrating collateral channels (arrows) which develop and which maintain circulation to the head and upper extremities.

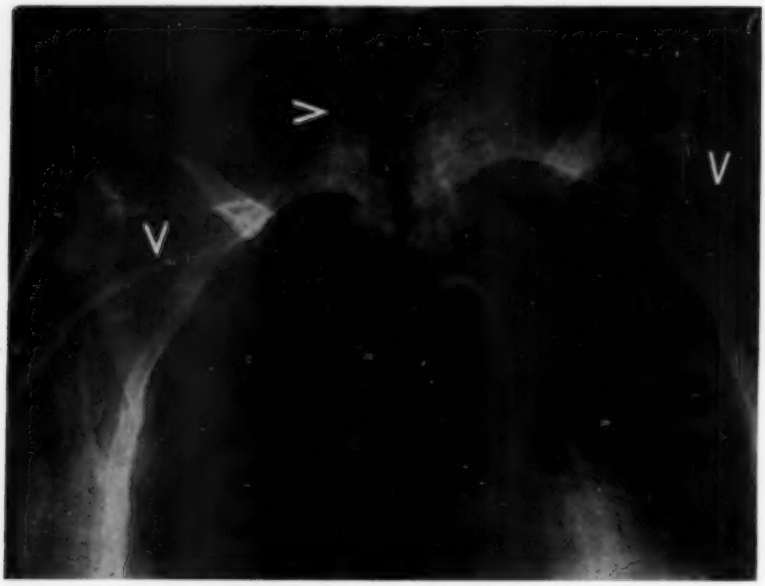

Fig. 4 (Tour and Hoyt). The final arteriogram in this series, showing eventual filling of the right common carotid and the right and left subclavian arteries (arrows) as a result of collateral circulation.

(Figure 5 is on the facing page)

Fig. 6 (Tour and Hoyt). Mobilization of the innominate (left) and the left common carotid arteries at the time of surgery.

Fig. 7 (Tour and Hoyt). Incision into the innominate and left common carotid arteries, showing thrombotic and arteriosclerotic debris visible in the former.

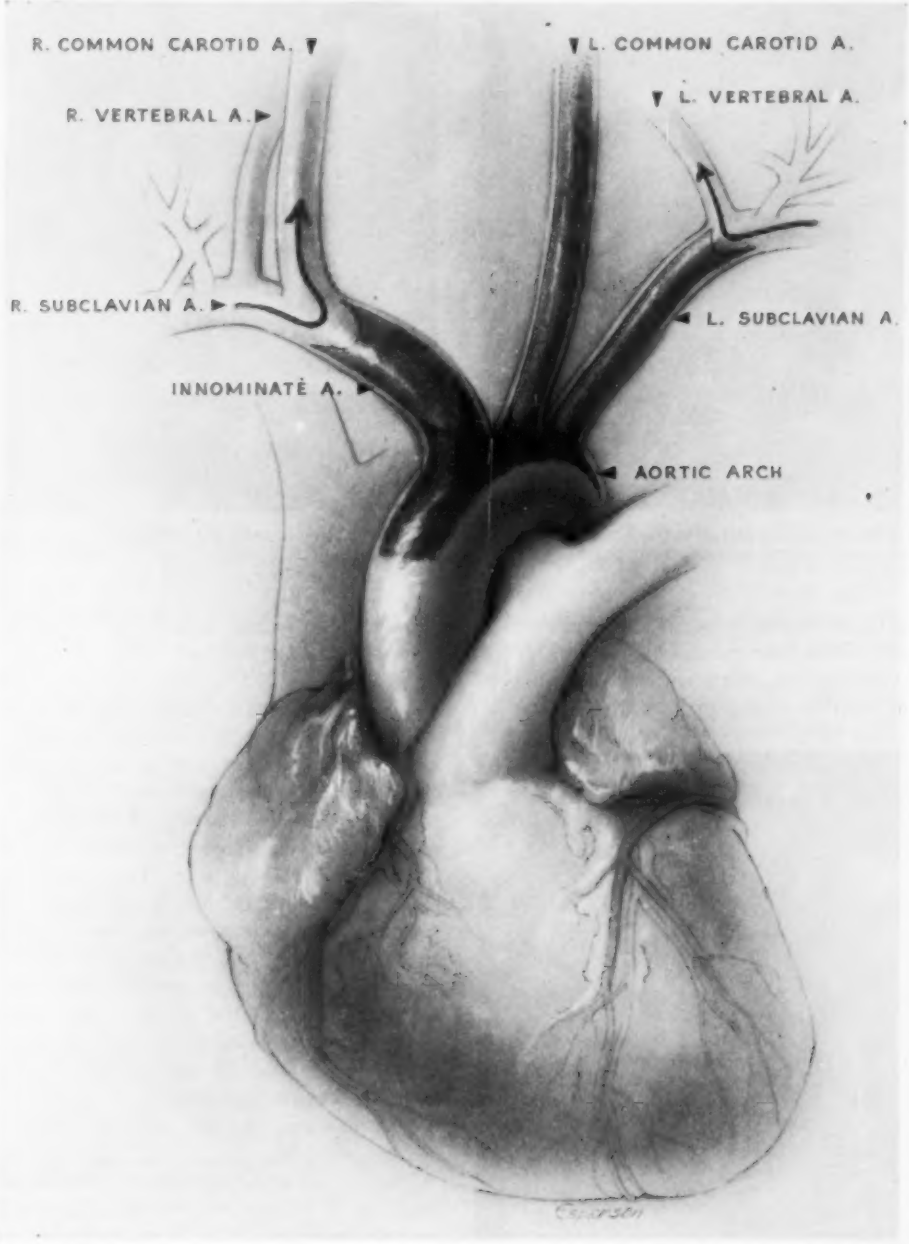

Fig. 5 (Tour and Hoyt). The aortic arch syndrome. Artist's drawing of the obstructions which were encountered at the time of surgical exploration. The anatomy of the area is shown, as well as the altered circulatory pathways. The stippled portions indicate sclerotic (dark) and thrombotic (light) occlusion.

Fig. 8 (Tour and Hoyt). The lumen of the innominate artery subsequent to thromboendarterectomy.

Fig. 9 (Tour and Hoyt). Final closure of the innominate and left common carotid arteries (the innominate vein being retracted).

nervous system most of the time, but the pressure in the carotid siphon was greatly reduced. The collateral circulation involved is from the descending aorta to the axillary and subclavian trunks and finally to the vertebral arteries and the right internal carotid artery.

Fig. 10 (Tour and Hoyt). Extraction of intima and organized thrombus from the left common carotid artery via an incision in the neck.

Under these circumstances, the ophthalmic artery is no longer a mainstem artery with a high pressure, but is a peripheral branch artery with low pressure. Certain peculiarities of the anatomy of the ophthalmic artery may also serve to embarrass the blood supply to the eye. These are the oblique "take-off" of the artery from the internal carotid, and the peculiar "intimal cushions" at the junction of these vessels (Böck and Schwarz-Karsten[32]). Since the oxygen demand of the retina is high, relatively minor changes in the altered blood supply to the head are apparently sufficient to cause changes in retinal function prior to the occurrence of any marked cerebral symptoms.

The re-awakening of interest in the measurement of retinal arterial blood pressure has closely followed upon the advances in the field of cardiovascular surgery. It provides a valuable and reliable tool for the evaluation of patients with carotid insuffi-

ciency, as reported by Heyman, Karp and Bloor,[33] Hollenhorst, Wilbur and Svien,[34] and Blodi and Van Allen.[35] Cases of the aortic arch syndrome demonstrate occlusion of both carotid arteries and one would therefore expect markedly lowered retinal arterial blood pressure readings on examination with the ophthalmodynamometer.

In the case just reported, these were 30 mm. Hg diastolic and 32 mm. Hg systolic. The low pulse pressure made it difficult to distinguish between the two readings and was evident if one applied light digital pressure to the globe while observing the fundus with the ophthalmoscope. This disappearance of the blood column was also noted by Ross and McKusick[13] and by Hollenhorst.[22]

Following surgical removal of the obstructions in the major vessels involved, ophthalmodynamometry provided dramatic evidence of the increase in retinal arterial pressure at a time when the carotid pulses could not be palpated because of neck dressings. The almost immediate rise of intraocular pressure from very low preoperative levels to almost normal was further evidence of the improved circulation to the head.

Summary

1. The signs and symptoms attendant upon obstruction of the great vessels arising from the arch of the aorta have been discussed, and the pertinent literature has been reviewed.

2. In order to simplify the nomenclature, we believe that the term "aortic arch syndrome" should be employed when referring to this condition.

3. The etiology of the disease is most often syphilitic aortitis, with or without aneurysm. The reported high incidence in young women, particularly oriental, is open to question.

4. The predominance of ocular involvement has been stressed. Characteristic findings include transient blindness, followed by such trophic changes as atrophy and neovascularization of the iris, iridoplegia, cataract, and retinal arteriovenous shunts.

5. A case has been reported which was successfully treated by surgical removal of obstructions in the major branches of the aortic arch. The value of tonometry and ophthalmodynamometry in the pre- and postoperative evaluation of the case is stressed.

6. It is emphasized that rapid advances in the field of cardiovascular surgery, with the aid of hypothermia, have greatly improved the prognosis.

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Medical Center (22).

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OBSERVATIONS ON RECURRENT EROSION OF THE CORNEA*

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Recurrent erosion of the cornea has been known under a variety of names, including "relapsing keratitis" and "finger-nail keratitis," the latter deriving from the peculiar frequency of the disease in parents scratched by their infants' finger nails. Most cases of the disease follow trauma but some few appear to arise spontaneously. A diagnostic feature of the disease is its recurrence at the time of the first opening of the eye in the morning. The epithelium is torn loose from Bowman's membrane and hangs typically in the form of an epithelial filament (fig. 1). The eye becomes red and exquisitely painful and tearing is profuse. After a few hours, the epithelium reforms and the eye

* From the Department of Ophthalmology and the Francis I. Proctor Foundation for Research in Ophthalmology of the University of California School of Medicine, San Francisco.

becomes white and comfortable, only to relapse at some later date. Secondary bacterial infection is a rare but important complication which can eventuate in scars and reduce vision.

No universally accepted theory[1] has been advanced to account for the poor union between the epithelium and Bowman's membrane which permits the periodic relapse. Duke-Elder[2] suggests that an "epithelial weakness is left owing to an irregular or unsatisfactory restitution of the terminal nerve filaments among the epithelial cells." The common method of treatment, namely, cauterization with tincture of iodine or other chemical, leaves much to be desired and may even lead to permanent opacification of the cornea.

The following observations of various aspects of the disease in a total of 32 cases have been collected over a 12-year period.

Fig. 2 (Thygeson). Biomicroscopic appearance (schematic) of persistent epithelial edema.

Clinical picture

With two exceptions, all the cases in this series were posttraumatic and all have followed the characteristic pattern of relapse on waking in the morning. Forceful opening of the lids seems to have been the precipitating factor. The site of the relapse has been regularly in the midline, just below the pupil, even when the original trauma has been in a different area. There is no ready explanation for this localization of the recurring lesion. Usually five or six hours from the beginning of the relapse have been required for epithelium to cover the defect but persistent edema of the epithelium (fig. 2) has been demonstrable with the slitlamp for many days or weeks.

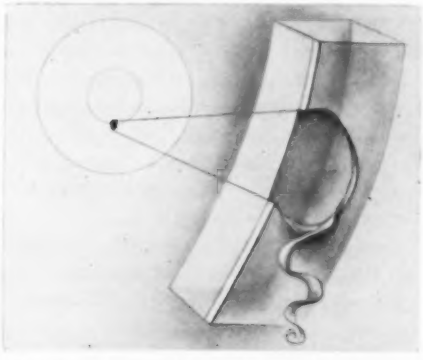

Fig. 1 (Thygeson). Biomicroscopic appearance (schematic) of recurrent erosion, showing filament formation.

In the one case that became secondarily infected, a pneumococcic ulcer developed which responded to antibiotic therapy but left a permanent scar. Frequency of relapse in previously untreated cases was reported by the patients as varying from several weeks to several months. One case had had nine relapses in spite of repeated cauterizations. It is of interest that the lesions were relatively uniform in size, varying from two to four mm. in width. In only one case was a larger erosion seen (fig. 3).

Previous trauma

In 30 of the 32 cases of this series there was either clear-cut evidence or history of previous eye injury. The remaining two pa-

Fig. 3 (Thygeson). Recurrent erosion located typically but of unusual size, stained with fluorescein.

tients, whose lesions differed in no way, denied having sustained any such injury. The 30 known injuries had one feature in common: extensive damage to the epithelium. Six mothers and two fathers had all been scratched by their children; four patients were struck while wearing glasses, and glass fragments had produced extensive epithelial damage; four patients (three of them secretaries) had been injured by glancing blows with stiff paper; three others were struck glancing blows by stiff wire. The remaining 11 patients had been injured by various objects, including brooms, various tools, thorns, and so forth, all of which had caused extensive superficial damage. It is of interest to me that over the years not one of my many cases of foreign bodies or cases of chemical injury has been followed, so far as I know, by recurrent erosion. It is of further interest that extensive removal of epithelium by cauterizaton or otherwise (a procedure of practical therapeutic importance in many cases of herpetic keratitis) has in my experience never led to recurrent erosion.

Therapy of recurrent erosion

The first 20 of my 32 cases were treated in the classical fashion by removal of loose epithelium and cauterization with tincture of iodine. The eyes were usually patched for several days or until there was good epithelial coverage of the affected areas. The results were good in 12 cases, no relapses occurring during observation periods of several months. In the remaining eight cases the results were unsatisfactory; further relapses occurred and additional cauterizations were necessary. In two cases cauterization was repeated three times before a cure was obtained; in each of these, corneal nebulae persisted and one developed the pneumococcic ulcer, previously mentioned, which led to further opacification. The reaction to cauterization varied greatly from patient to patient, some showing very little and others a great deal; one young mother was twice incapacitated for several days by her severe reaction to iodinization.

The remaining 12 cases in the series were all treated by the instillation of a steroid suspension or solution* every few hours during the day for the first 48 hours, or until the epithelium was again intact, without patching of the eye. In the first few cases treated by this method, the epithelial filament, when present, was removed mechanically; in later cases it was ignored. After the epithelium appeared to be intact, the steroid instillations were discontinued and treatment was limited to the use of five-percent boric-acid ophthalmic ointment at night for the purpose of minimizing the pull on the epithelium on waking. In addition, the patient was cautioned to open his eyes slowly and gently for the first week or two after the relapse. The cornea was observed at intervals of a week or two for signs of edema in the affected area. Persistent edema was almost the rule but its duration varied from a few weeks to two months in one case. The boric ointment was continued nightly arbitrarily for one month after the edema had disappeared. Under this regime there have been no relapses to date.

This treatment with a steroid suspension (or solution) and boric-acid ointment has appeared to have a number of advantages

* Two and one-half percent cortisone acetate ophthalmic suspension was employed in the first four cases. Other steroid preparations have been used subsequently with equally good results.

over the cauterization method. It has prevented damage to the stroma, has avoided the inflammatory reaction incident to the use of a cauterizing agent, and so far has resulted in a higher percentage of clinical cures.

Prevention of recurrent erosion

Since the type of corneal injury most likely to develop recurrent erosion is now well recognized, it seemed logical to try the use of a steroid solution and boric-acid ointment prophylactically. At the time of writing, only 11 patients with predisposing corneal injuries have been available. All were treated in this way and so far none has developed recurrent erosion during observation periods ranging from two years to three months. Unfortunately, no figures are available to indicate the number of relapses which could have been expected without any prophylaxis. Personal experience over the past 30 years, however, has led me to expect at least a 25-percent incidence of recurrent erosion subsequent to this type of injury.

Discussion

Although the underlying mechanism which induces recurrent erosion is not yet understood, certain facts are known about the disease. It seems certain that relapses are associated with persistent epithelial edema and that the edematous epithelium is pulled loose from the stroma by the suction effect produced by the sudden opening of the lids. This suction effect is probably enhanced by prolonged lid closure during sleep and by the paucity of night-time tears. It seems logical, therefore, to use as simple a method as possible to reduce epithelial edema and prevent the suction on waking. Steroids were employed primarily for the purpose of reducing inflammation and secondarily for their effort in slowing epithelial proliferation, since overgrowth of epithelium with filament production has been a feature of some cases of the disease. The bland ointment was used to minimize the suction effect of sudden opening of the lids by providing an oily film between the epithelium of the lids and cornea.

The two cases of recurrent erosion without previous history of trauma were intriguing. Is it possible that minimal trauma had occurred without the patient's knowledge, or did the epithelium become edematous through some endothelial damage such as may obtain in an early endothelial dystrophy? In these two patients no signs of endothelial dystrophy were apparent after recovery; in my experience, moreover, endothelial dystrophy has not predisposed to recurrent erosion.

Conclusions

1. Thirty-two cases of recurrent erosion are reported; 30 of them followed corneal injury with extensive damage to the epithelial surface; two had no previous history of corneal injury.

2. The same clinical picture was observed in all 32 cases: the lesion was situated just below the pupil in the midline, irrespective of the site of the original injury, and recurrences always took place at the time when the lids were first opened in the morning. In only one case was there a complicating secondary bacterial infection.

3. Treatment by chemical cauterization of the first 20 cases led to cures in 12 and to relapses in eight, which then required further cauterization.

4. Treatment of the last 12 cases with topical steroids (in suspension or solution) for the first few days, and with a bland ointment at night until all epithelial edema had disappeared, was effective; no relapses have been noted to date.

5. Prophylactic treatment with a topical steroid and a bland ointment has been tried in 11 cases of corneal injury of the type expected to lead to recurrent erosion. None of these cases has so far developed the disease.

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CYTOMEGALIC INCLUSION DISEASE

REPORT OF A CASE

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Cytomegalic inclusion disease, a virus disease which affects many organs of the body (salivary glands, lungs, liver, kidneys, pancreas, brain, thyroid and pituitary glands, eyes) occurs most commonly in the newborn, although it may affect any age group. Since the early part of this century, when the first description of the disease appeared, the condition has been increasingly recognized, until now the clinical and pathologic pictures are fairly complete.

Clinically it may appear as an acute or subacute febrile illness. Christensen has outlined various clinical manifestations and discusses the vital structures most frequently involved.

In infants the clinical manifestations of the disease are characterized by prematurity, jaundice, bleeding tendencies, progressive pneumonia, splenomegaly, hepatomegaly, and neurologic disturbances.

Potter has shown that it is possible for a pregnant woman to harbor a virus which may produce a fatal disease in her offspring without herself manifesting any evidence of disease. Potter also believes that when characteristic findings are present at birth, the infection probably occurred early in intrauterine life.

In the differential diagnosis, it is necessary to distinguish cytomegalic inclusion disease from toxoplasmosis, especially in the presence of cerebral calcification. In toxoplasmosis, calcification usually appears at a later date, is less extensive, and its location more variable. In any case in which cytomegalia is considered, the urine should be examined for typical cells. The methylene-blue dye test is negative in cytomegalic inclusion disease, except in the first six months, when there may be a low titer due to passive transfer from the mother. The dye-test titer of the mother, therefore, is important in the diagnosis.

Pathologically, the disease is recognized by inclusion-containing giant cells which appear predominantly in the epithelial linings of the visceral and cerebral epithelium. Megalocytes contain both cytoplasmic and intranuclear inclusions, and are found in the brain, lung, liver, kidney, and so forth.

According to Christensen, in the fully developed cell, the nuclei are oval, measuring 10 to 15 μ in diameter, and are eccentrically placed. The nuclear inclusions lie centrally and stain deeply. They are often separated from the nuclear membrane by a clear zone and the remaining nuclear material forms a thin rim around the periphery. The cytoplasmic inclusions are smaller and less distinct. They usually assume a crescentic pattern and have a powdery appearance.

Although the virus has a preference for epithelial cells, it may appear also in endothelium (Haymaker). Most often, it is found in cells lining the ducts of various organs, such as the alveoli of lungs and tubular epithelium of the kidney. In the tissues these inclusion-bearing cells are often accompanied by an infiltration of lymphocytes, macrophages, and reactive fibrosis. In the kidney the cells slough into the urinary tract and may be demonstrated in the urine. Weller and associates have recovered the virus in tis-

sue cultures of fibroblasts after aspiration biopsy of liver.

McElfresh, et al., reported three cases of cytomegalic inclusion disease: One patient, aged six weeks, appeared blind and there was no pupillary light reaction. The fundi, however, revealed no abnormalities. Five months later fundus examination revealed a round well-circumscribed patch of lighter color in the right choroid. The eyes were not examined at autopsy.

Weller and associates reported isolation of intranuclear inclusion-producing agents from the urine of three infants suffering with illnesses resembling cytomegalic inclusion disease. One of the infants had chorioretinitis in addition to hepatomegaly and cerebral calcification. The infant with chorioretinitis was studied further by Burns.

Burns, on second trial, isolated an agent from the anterior chamber which produced inclusions in tissue culture similar to those previously isolated from the urine. This evidence tends to establish the viral etiology of the ocular disease. He suggests that cytomegalic inclusion disease be considered as a cause of uveitis in children and should be considered with toxoplasmosis in the differential diagnosis of uveitis associated with cerebral calcification.

Foerster reported inclusion body retinitis in an enucleated eye of a 59-year-old white woman.

Guyton reported the existence of chorioretinitis in a case of generalized cytomegalic inclusion disease, first noted at the age of six weeks. Chorioretinitis and intracranial calcification were present.

Case report

History. A 20-year-old primigravida mother had an entirely normal prenatal course. Upon admittance to West Suburban Hospital, Oak Park, Illinois, the fetal heart beats were not audible. There was no bleeding on admission or during the course of labor. She gave birth to a stillborn infant which was premature and macerated.

Necropsy report. The infant of 34 weeks' gestation weighed 1,590 gm. and measured 36 cm. in length. The brain revealed dilated ventricles which were filled with fluid and the tissue showed numerous small yellow areas. The walls of the brain were soft and pinkish gray; the inner surface was finely granular, rough, and speckled with numerous yellow areas. There were a few places of calcific material measuring up to 0.5 cm. in the greatest dimension.

The heart revealed no abnormalities. The lungs were noncrepitant and a dark purplish red. The spleen was enlarged and dark red. The liver was slightly enlarged and a dark reddish brown, as were the kidneys. The adrenals were a yellowish tan. The pleural and abdominal cavities contained bloody fluid.

On microscopic examination, all tissues showed numerous very large mononuclear cells containing inclusions both in the cytoplasm and in the nuclei. The initial diagnosis of toxoplasmosis was, on further study, changed to a cytomegalic salivary virus inclusion disease.

The eyes were given to me by Dr. John Kiselis and were sectioned in the Eye Pathology Laboratory of the University of California School of Medicine, where the inclusions caused great excitement (fig. 1). It was agreed by Dr. Phillips Thygeson, Mrs. Foerster, and Dr. Robert Cello that this was an inclusion virus disease.

The findings in each of the eyes are similar. The cornea and sclera show no gross abnormalities; the canal of Schlemm is open, and the trabeculae

Fig. 1 (Theobald). Section of globe with cytomegalic inclusion disease.

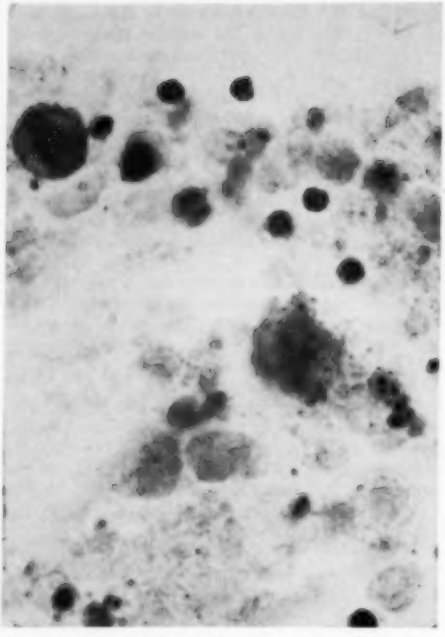

Fig. 2a (Theobald). Broken-up nuclear inclusions of the retina (Masson's stain).

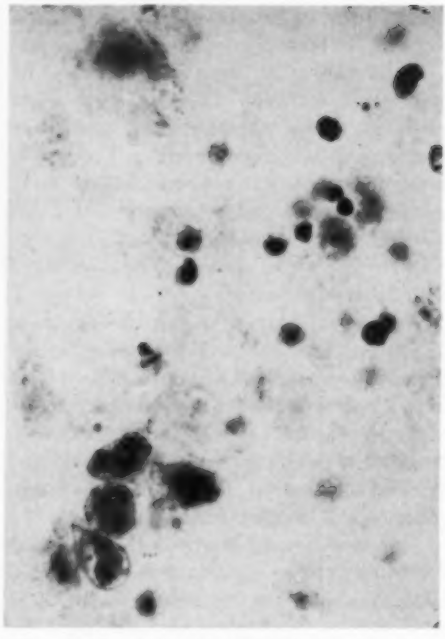

Fig. 2b (Theobald). Nuclear inclusions in retina (Masson's stain).

fairly well developed. The anterior chamber is deep in most sections, but in some is obliterated centrally by the iris which is displaced forward by the round cataractous lens.

The iris, ciliary body, and choroid are compact, and their vessels are filled mostly by nucleated cells. The pigment epithelium over the anterior uvea has disintegrated and migrated, especially where there is evidence of chorioretinitis.

The retina (figs. 2a, 2b, and 2c) is necrotic, and only small segments remain where the nuclear layers can be recognized. In the necrotic retina are seen many large monocytes which contain inclusions in either the cytoplasm and nuclei, or both. The inclusions are of different types—the ones in the cytoplasm are quite large, and the broken-up ones in the nuclei have a powdery appearance.

In the hematoxylin-eosin sections, the inclusions show faintly, but with PTAH, PAS, and Masson's trichrome stains they appear with startling clarity. PAS brings out cytoplasmic inclusions in the lung (fig. 3a) as well as Type A nuclear inclusions (fig. 3b), and Masson's stain brings out (bright red) intranuclear bodies in the retina. Very occasionally a cell is seen with inclusions resembling toxoplasmosis. There are areas of calcification. The

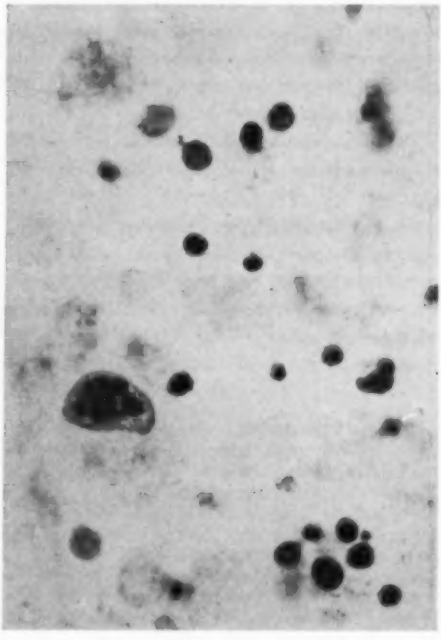

Fig. 2c (Theobald). Necrotic retinal lesions. Inclusions resembling toxoplasmosis (Masson's stain).

sclera and optic nerve show nothing of note. It is of interest that inclusions are found only in the retina in these eyes.

Dr. Thygeson's feeling was that this was an inclusion virus disease, but he was of the opinion that it was not the usual cytomegalic inclusion of the newborn. He felt the inclusions somewhat resembled those seen in yellow fever but he did not suggest that the disease is yellow fever.

Dr. Robert Cello, a veterinary ophthalmologist, has been doing special slides on distemper. He reported that the inclusions in this case appeared similar to those of distemper. According to Dr. Cello, in distemper, the cytoplasmic inclusions are more apt to occur in the cells seen in the lung, and the nuclear inclusions in the retina.

Slides from this case were presented at the *Uveitis Symposium* sponsored by the Sloan Foundation at Princeton (1958). No definite opinion was given as to the type of virus which produced these inclusions.

Discussion

It has long been known that virus infections can be transmitted from mother to fetus. That certain viruses may affect the very young infant and produce characteristic lesions is also well known and reports of such virus infections are becoming more numerous. Other conditions thought to be viral in nature because of the presence of intranuclear inclusions have also been observed, especially in the lungs.

Perhaps the involvement of the eyes by virus inclusion disease is more widespread than medical literature indicates; general pathologists are seldom interested in eye pathology. Involvement of the eye has been reported in only a few cases. In his paper, Christensen concluded that cytomegalic inclusion disease is a disease entity of increasing importance . . . the clinical findings simulate toxoplasmosis and possibly measles in the first trimester. These include retinopathy, intracranial calcifications, and cataracts.

It has been reported that the disease has a predilection for brain tissue and the child who survives may be mentally retarded. However, the mother of such a child may subsequently give birth to a normal infant.

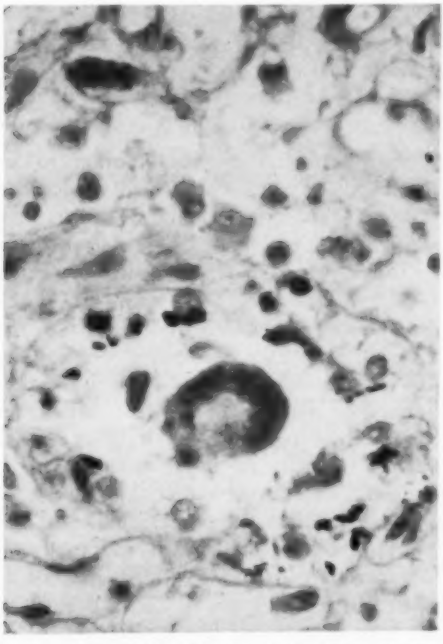

Fig. 3a (Theobald). Cytoplasmic inclusions in the lung (PAS).

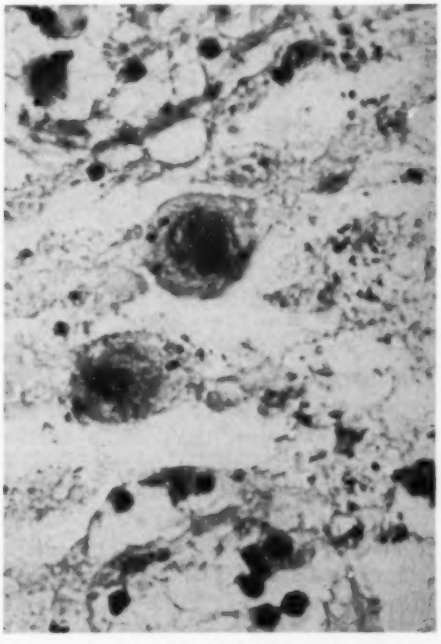

Fig. 3b (Theobald). Nuclear inclusions in the lung (PTAH).

SUMMARY

A case of virus inclusion disease in a stillborn infant is reported. The eye findings include cataract, necrosis of retina, and very large mononuclear cells in the retina containing cytoplasmic and nuclear inclusions.

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MODIFIED KNIFE AND TECHNIQUES FOR DISCISSION*

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Congenital cataracts, their types and surgical treatment have been subjects of great interest and concern to Frederick C. Cordes. In his Jackson Memorial Lecture, Cordes[1] documented early and late complications of congenital cataract surgery and correlated them with the type of operation. His findings indicate that from the view point of complications, multiple discissions are the least desirable of all procedures; however, as Cordes has noted, there are, in addition to after-cataracts, some congenital cataracts which are not amenable to linear extraction or types of operation other than discission It is not my intention to discuss the specific indications for discission. In this tribute to Frederick C. Cordes, I have chosen to describe a knife and some modifications in the techniques of discission which reduce the incidence of complications which he has studied so thoroughly.

This report is based upon experience in the Children's Eye Clinic, sponsored at the University of Oregon Medical School by the Oregon State Elks Association. Since 1950, 106 discission operations have been performed by me and the resident staff under my direct supervision. In addition, it has been possible for me to see on a referral or consultation basis an appreciable number of patients with congenital cataracts who have been operated by others. This experience indicates that discission is still the operation of choice in certain types of cataract and that, when it is indicated, the incidence of complications and sequelae can be reduced; how-

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ever, detailed statistical analysis of these case data will not be available for another decade. This is so because, as pointed out by Cordes,[1] 20 years or more may elapse before the onset of complications such as retinal detachment in these eyes.

First consider currently used techniques of discission. Judging from the literature and discussions with surgeons at other institutions, the most common procedure involves introduction of a knife blade into the anterior chamber by a puncture wound through peripheral cornea. The corneal wound then is used as a fulcrum as incisions are made into the lens or after-cataract. When the operation is used as a primary procedure to expose the cortex and nucleus to the aqueous, a large opening is made in the anterior capsule but the knife generally is not carried completely through the posterior capsule. The Ziegler technique of cutting completely through a congenital cataract into the vitreous now has few advocates; however, the Ziegler knife remains the most widely used type. According to one manufacturer of surgical instruments their distribution of Ziegler knives exceeds the combined sales of all other types.

In the treatment of membranous cataracts and after-cataracts the technique and knife devised by Wheeler[2] is sometimes preferred by Cordes[3] and a number of other experienced surgeons but apparently the operation is losing popularity. Among 22 American Board of Ophthalmology candidates queried in 1958, only eight were familiar with the technique and only four actually had been instructed to perform the operation during their residencies.

At the University of Oregon Medical School, both the Ziegler needle knife and the technique of using it have been modified in an effort to increase the efficacy of the procedure as well as to minimize its complications, As pointed out by Cordes,[1] the incidence of complications increases with the number of discissions performed on a particular eye. For this reason every effort should be made to perform the operation adequately on the first attempt. In my experience untimely loss of the anterior chamber has been the single biggest factor requiring the surgeon to withdraw the blade before he has achieved the desired result. A flat anterior chamber makes it unsafe to manipulate the knife and the softness of the eye makes it difficult to cut through or into a tough membrane. Then as the blade is withdrawn, the corneal endothelium and iris are endangered. It seems imperative that the shaft of the knife should fill the corneal or limbal incision so that there is no escape of aqueous as the blade is manipulated in the anterior chamber. The surgeon then can perform the operation unhurriedly and make multiple cuts or change the position of the blade if necessary.

For several years it has been possible to obtain Ziegler knives with a shaft of proper thickness to fill the puncture wound; however, the shape of the blade contributes to complications. There is a prominent heel at the shaft end of the blade which requires that the knife be withdrawn on the same plane as it was inserted; otherwise, the corneal opening will be enlarged by the blade. A far more important objection to the heel of the knife is that it may draw lens material or peripheral iris into the wound. Cordes[1] has called attention to iris incarceration into the wound as a cause of both peripheral adhesions favoring obstruction of the chamber angle and pupillary irregularities and displacement. In one of the eyes which he described there was an epithelial downgrowth.

It has been my experience that the dragging of a piece of capsule into the wound on the heel of the Ziegler knife is as significant as iris incarceration. It invariably leads to distortion of the pupil and if it extends completely through the wound, a tract is established for epithelial ingrowth.

Figure 1 illustrates such a circumstance. It is the eye of a child who had a discission for congenital cataract by a competent sur-

Fig. 1 (Swan). Epithelial cyst which developed after discission with a Ziegler-type knife. The surgeon noted that a strand of lens capsule had been pulled into the corneal puncture wound by the heel of the blade. This picture was taken one and one-half years after surgery.

geon. After the operation the surgeon noted that a strand of lens capsule had been drawn into the corneal wound by the heel of the Ziegler knife. He left the strand alone because the visual result seemed good and the wound seemed to be healing well. The child was not examined until a year and a half later when she was admitted to the Children's Eye Clinic at the University of Oregon Medical School. A typical epithelial cyst was found to fill one fourth of the anterior chamber and the ocular tension was elevated.

Another child has been observed in our clinic with an epithelial cyst developing after discission, but it has not been possible to determine the type of knife used.

In a number of other eyes I have observed strands of capsule to run from the pupillary area to the point of corneal or limbal puncture. Several have been observed with adherence of the iris to the cornea. In all such eyes the pupil has been distorted. For these reasons I do not believe that the Ziegler or other types of knife with the heel on the blade should be used for discission.

Several discission knives have been available which do not have a heel where the blade joins the shaft. These include the Knapp, Haab, and Curran knives but these knives do have a prominent convex cutting edge. As a result, these blades are relatively wide. It is my belief that the blade should be as narrow as possible to minimize the size of the opening in the cornea or limbus and, thereby, to prevent escape of aqueous when the blade is withdrawn. It is noteworthy that Cordes[1] found a high incidence of peripheral anterior synechia after discission operation, a finding which he believes may be accounted for by postoperative shallow chambers. The smallest possible puncture wound would be made by a knife with a straight blade continuous with a narrow shaft. Such a straight narrow blade passes through the cornea or limbic stroma and into a tough lens membrane with less resistance than with a wider convex type of cutting edge. Also, the narrow straight blade can be withdrawn without appreciable loss of aqueous or production of a wound large enough for incarceration of lens material or iris.

There are two other important aspects of discission knife design. One concerns the length of the blade. Several knives designed years ago, but still in use today, have blades five to seven-mm. long. In the past this length of blade was considered essential for the Ziegler technique of cutting completely through the lens because it was neccesary to have a blade with a cutting edge at least as long as the full thickness of the lens. Also, many surgeons have preferred the five to seven-mm. blade because it permitted a large cut to be made in an after-cataract with a single movement of the knife. Neither reason seems valid now.

To minimize vitreous damage and to maintain its support, the opening in an after-cataract should be just large enough to permit vision; that is, 1.5 to 2.0 mm. in diameter. Nothing is to be gained by a gaping opening which occupies the entire pupillary area and extends into the vitreous.

In my experience a cutting edge does not need to be longer than 3.0 mm. In fact, this shorter blade has several advantages. The surgeon is better able to judge the depth of penetration of the blade into a membrane or lens. The cutting edge can be kept in a small area and is less apt to cut the iris at the

pupillary margin. Its direction and position can be more readily changed than is possible with a longer blade. This is of great importance when discission is used as the major procedure or as a preliminary to linear extraction in those congenital cataracts which have a considerable amount of clear cortex surrounding a central opacity. Then the purpose of the operation is not only to open the anterior capsule but also to break up the cortex and nucleus by multiple cuts which do not penetrate the posterior capsule. Both rate and completeness of absorption of the lens material are proportional to the amount of lens substance exposed to the aqueous. It is almost essential to use a short blade which can be readily manipulated within the lens.

A final point of knife design concerns the polish and caliber of the shaft. I have already emphasized that the shaft should fill the puncture wound so that the aqueous cannot escape while the blade is in the anterior chamber and that both blade and shaft should be narrow to minimize the size of the corneal or limbal wound. It seems important that the shaft also be of constant caliber and be so highly polished that it slides easily through the corneal or limbal incision in case the surgeon wishes to extend or retract the blade in the anterior chamber. This is not possible without escape of aqueous if the shaft is tapered as in the Knapp type of knife.

A knife with the desirable characteristics which I have described has been made for the University of Oregon Medical School by the Storz Instrument Company at St. Louis (fig. 2). This knife has been in use at the University of Oregon Medical School Clinics and Hospitals for the past several years. It seldom has been necessary to perform more than two discission operations on any one eye, even when no other type of operation has been performed. The anterior chamber rarely has been lost during the operation and there have been no cases of persistent shallow chambers after surgery. Iris

Fig. 2 (Swan). As compared to the Ziegler knife (above), the modified knife (below) has a short, narrow blade which is continuous with a shaft of small caliber. It passes through the tissues with little resistance. The shaft is highly polished and untapered and fills the wound in the limbus or cornea; therefore, the blade can be manipulated in the anterior chamber without aqueous loss. The blade has no heel which might pull iris or lens material into the puncture wound as the knife is withdrawn.

incarceration with pupillary distortion or incarceration of lens material in the incision has not occurred. The technique at the University of Oregon Medical School now will be summarized.

Maximal mydriasis always is obtained by using a combination of drugs which stimulate the iris dilator and induce paresis of the iris sphincter. In children the operation is performed under moderately deep general anesthesia. I emphasize this point because the discission operation often may be accomplished in a matter of seconds; consequently, in many institutions only a light anesthesia is induced and the operation then is performed quickly before the child awakens. This may be permissible in some cases, but in most other young patients the anesthesia should be adequate to permit a thorough examination of the eyes as well as an unhurried operation.

As many patients with congenital cataracts are either too young to co-operate or have gross nystagmoid movements, anesthesia is essential to examine the eyes completely and to take photographs for future reference. For these purposes a microscope with a through-the-lens illumination system and camera attachment is of great value. The lens or after-cataract, iris, and cornea are studied under high magnification with diffuse axial illumination and the usual oblique slitbeam. Gonioscopy is essential to determine the presence or absence of peripheral

anterior synechia in eyes which have had surgery.

In view of the relatively high incidence of secondary glaucoma after discissions and linear extractions, it is imperative that ocular tension studies be made even though allowances must be made for alterations induced by the general anesthesia. In several instances the finding of a difference in ocular tension in the two eyes of two to four mm. has given me a forewarning of secondary glaucoma. If funduscopy is possible, attention is paid to the status of the vitreous as well as to the posterior segment.

How should the globe be fixed for the discission operation? Some surgeons prefer to have an assistant help stabilize the globe by sutures or forceps but I feel that it is advantageous for the operator to have complete control of the eye so that he can change its position if this should become necessary during the operation. For this purpose I have found the O'Brien fixation forceps to be highly satisfactory. They have angled-teeth like the Elschnig forceps but are more delicate so that scleral fixation can be obtained near the limbus with relatively little distortion of the globe. To avoid increasing ocular pressure by the tension of the forceps, the scleral bite should be small so that the sclera is not pinched into a fold.

The site of introduction of the needle knife into the anterior chamber merits some discussion. Judging from the literature, a slanting puncture wound through the temporal periphery of clear cornea has been preferred. There are several advantages to such a puncture wound. There is no danger of bleeding and there is rapid closure of the puncture wound due to imbibition of the fluid by the corneal stroma. The advocates of this approach also state that the knife can be introduced at a better angle for cutting through a tough membrane or for cutting the anterior capsule and breaking-up of the cortex in a primary needling of the lens. It is my belief that, with exception of the Wheeler operation, there are important advantages to the translimbal introduction of the needle knife. No scar is made in the cornea and there is less chance of creating either an adherent leucoma or an epithelial ingrowth.

This point of entry of the knife in the limbus also gives a surgeon greater freedom of movement within the anterior chamber than is possible through a more central corneal incision. Furthermore, the blade is more parallel to the face of the vitreous so that there is less danger of accidentally cutting into it.

To reduce the risk of epithelial ingrowth and to protect the stromal puncture wound with a flap, the conjunctiva and Tenon's capsule are picked up on the tip of the knife one and one-half to two mm. behind the junction of the limbal epithelium and clear cornea. The tip of the blade is then slanted forward under the epithelium to reach the limbal stroma.

The slanting incision through the stroma enters the anterior chamber in the region of Schwalbe's line. The blade sometimes passes through some of the episcleral vessels but it is in front of the deep scleral plexus; consequently, bleeding into the anterior chamber is rare.

The actual discission varies with the type of cataract or character of the after-cataract; however, I feel strongly that use of the corneal or limbal wound as a fulcrum has been unduly emphasized and often leads to injury. This maneuver is permissible only if a delicate membrane is being cut or if soft lens cortex and nucleus are being cut up and stirred as advocated by Moncreiff.[4]

I find that there is a tendency for inexperienced surgeons to use routinely the limbal or corneal puncture wound as a fulcrum and to manipulate the knife without any type of slicing motion even through tough membranes. The result is often a tearing and displacement of tissues rather than a precise and relatively atraumatic cutting. A great deal of traction on the vitreous, iris, and ciliary body can be induced by leverage

on the knife if the tip is caught in the lens or a tough after-cataract. I have seen the lens dislocated by this maneuver.

I do not wish to imply that a slicing motion of the knife always is indicated. For example, in the treatment of after-cataract, collections of Elschnig's pearls may block the pupillary opening. The tip of the knife can be used to gently dislodge these bodies from the visual axis. Then some cataracts may consist only of the posterior capsule and a few lens remnants. A two to three-mm. opening along the visual axis is all that is necessary to obtain good vision.

The line of fixation is determined preoperatively; then, the tip of the knife is used to scratch a hole in the after-cataract in the desired area. Often this can be done without rupture of the vitreous face. A desirable postoperative finding in such cases is a tiny knuckle of vitreous bulging into the anterior chamber. This maintains the opening in the after-cataract.

I believe that, for the average operator, the "scratching" technique with the tip of the needle knife is a safer and more predictable operation for after-cataract than is the Wheeler maneuver. The Wheeler technique is a highly effective means of cutting through a relatively dense membrane when the maneuver is properly executed; however, I find it difficult to teach to the average resident who now has relatively little opportunity to operate after-cataracts. Also, the operation is apt to produce a larger hole in the after-cataract than is desirable and some cutting into the vitreous is unavoidable.

My final point concerns removal of the knife from the anterior chamber. I have noted residents and even some experienced surgeons to remove the blade with a quick jerk hoping to minimize escape of aqueous. Precipitous removal of the blade is apt to result in a cutting injury to the iris and corneal endothelium or accidental enlargement of the corneal wound. With the technique and knife that I have described, removal of the blade can and should be done unhurriedly. In recent years there have been no cases of delayed reformation of the anterior chamber after discission on the University of Oregon services. It has not been necessary to inject air into the anterior chamber.

Summary

In his Jackson Memorial Lecture, Dr. Cordes emphasized that complications are prone to occur after multiple discissions for congenital cataract and after-cataract. It has been the purpose of this report to describe some modifications in technique which reduce the number of discissions required, and the incidence of complications, when this operation is indicated.

A discission knife has been designed which has the following desirable characteristics. The blade is narrow because the cutting edge is continuous with a shaft of small caliber and high polish. This reduces resistance to passage of the knife and minimizes loss of aqueous. Also, there is no heel or convex blade which might catch and draw iris and lens material into the corneal or limbal incision as the knife is withdrawn. The cutting edge is short to give the surgeon more freedom to manipulate the knife in the anterior chamber than is possible with standard type five to seven-mm. blades. The shaft of the blade is of small caliber, untapered, and of a size which plugs the opening made by the knife blade. As a result there is no escape of aqueous around the shaft, so the operation can be performed unhurriedly, and the knife withdrawn without loss of the anterior chamber. In the past, escape of aqueous before the surgeon has achieved the desired result has been a major factor contributing to complications because it has necessitated reoperation as well as causing those undesirable effects attributable to loss of the anterior chamber.

Recommended procedures are described. Anesthesia should be adequate both for a thorough pre-operative examination and an unhurried operation. Examination should in-

clude biomicroscopy, gonioscopy, tension studies, and photographs. Without anesthesia these procedures usually cannot be performed well on infants or older children with gross nystagmoid movements. Maximal mydriasis is obtained. Scleral fixation is made by using the O'Brien type forceps. A narrow bite is used to avoid increased intraocular pressure. The eye is entirely under the control of the surgeon.

To eliminate corneal scars, adherent leukoma, and epithelial ingrowth, the knife is introduced into the anterior chamber by a slanting puncture wound made through limbal stroma under conjunctiva and Tenon's capsule. This approach allows maximal room to manipulate the blade and keeps it nearly parallel with the vitreous face. The actual discission varies with the type of cataract or after-cataract, as well as with the purpose of the operation. When discission is indicated as a primary procedure, or as preliminary to linear extraction, the point of puncture of the limbus can be used as a fulcrum to open the anterior capsule and to cut up soft clear cortex in all parts of the lens; however, routine use of the fulcrum technique for all types of cataract is deplored. It often results in tearing and displacement of the lens or after-cataract. The knife, described above, slides easily in the limbal stroma and permits the surgeon to use a back-and-forth slicing motion to open a tough membrane. On delicate membranes the tip of the knife can be used to scratch a small opening along the visual axis. This seems preferable to the Wheeler maneuver because it is technically easier and results in little or no vitreous disturbance.

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A REVIEW OF DATA ON THE OCCURRENCE OF GLAUCOMA*

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Introduction

When a prevention of blindness project was established in the California State Department of Public Health, provision was made to apply the investigative tool of public health—epidemiology—to blindness. The purpose of this paper is to present some ideas about the application of this tool to glaucoma and to review what has been observed and recorded about the natural occurrence of this major cause of blindness.

On a grant from the W. K. Kellogg Foundation the project has sought to establish the amount, nature, and distribution of the various causes of blindness and, on the basis of these findings, to demonstrate a preventive program.

A first step in the public health assessment of blindness was to gather and analyze data on the occurrence of blindness by time and place, by causes, and by characteristics of the affected persons in the population. Such

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A major share of the review of the literature and the abstracting of articles for inclusion was done by Miss Dorothy H. Fowler, formerly research technician with the project. Assistance was provided in classifying and selecting the material for discussion by Robert M. Drake, M.D., formerly of the Bureau of Chronic Diseases staff in the California State Department of Public Health.

studies done by the project staff, together with other information, pointed to glaucoma as a major cause of blindness in need of investigation.[1] It was understood that glaucoma is a term which includes the primary, secondary, and congenital glaucomas.[2] Our interest for investigation centered on the primary glaucomas, now classified as angle-closure and open-angle.

From the standpoint of preventive measures the two problems presented by the most frequent type of glaucoma, open-angle, are the need for early detection and further search for causes. Epidemiologic studies may offer promise in dealing with both problems. Measurement of intraocular pressure has been applied in recent years as a screening technique for early detection. Used on more or less random samples of the adult population about two percent of those screened are found to have glaucoma.[3-5] Even with this detection rate it has been said that mass screening is impracticable.[5] Physicians are urged to do tonometer measurements on all persons over 40 years of age as part of the routine examination of the patient.[6] Whatever the ultimate pattern for early detection of glaucoma its effectiveness can be improved if individuals and population groups at increased risk can be more precisely identified. This will allow concentration of effort with maximum results rather than carrying out surveys on random groups. Identification of these groups is a useful function of that study which is focussed on the occurrence of disease among people.

Since the search for causative factors remains the most important function of epidemiology some application of this method of study is warranted to complement the considerable research being done by clinical and laboratory methods. The delineation of persons at increased risk (or at reduced risk) of acquiring a disease is an elemental epidemiologic consideration and it may (and often has, for example, retrolental fibroplasia) help point to causes.

An accepted method for studying epidemic occurrence, in recent years Gilliam,[7] Clark,[8] Dorn,[9] Dyar and Breslow,[10] and Morris,[11,12] have discussed the uses and limitations of the epidemiologic method applied to non-infectious diseases.

The steps in systematic investigation of chronic diseases are based on the premise that some of the diseases are associated with social, environmental, and other factors frequently overlooked in clinical investigation. In applying this systematic method of inquiry to glaucoma the first step includes a review of the available knowledge about the kind of people who have glaucoma—their age, sex, race or ethnic group, socio-economic status, occupation, nutrition, geographic distribution, and other groupings that may have been observed and recorded. It also includes obtaining data on the trend of the disease occurrence over as long a time period as available. The various hypotheses on causation are studied with particular attention to the data supporting the theories, such as the population groups studied, the manner in which data were collected, and the methods of analysis. In addition to noting the nature and adequacy of available knowledge, this first step of description allows an assessment of the gaps in the available information.

Such a review of the literature has been undertaken and is presented here. In terms of the volume of articles read, abstracted, and classified the review is felt to be reasonably adequate. However, as is always the case whenever a line must be drawn by available time, the last article opens up almost as wide a field for further reading as did the first title. The most serious limitation has been in searching the foreign language periodicals. Here reliance had to be on brief items from the medical abstract journals or on the expectation that important contributions to the glaucoma literature would be noted in the annual reviews of the subject. The present paper is not presumed to be the result of a critical reading but rather an attempt to get in one place what has been said and on what bases. Therefore every

contribution has been included which met the test of providing supporting data to conclusions reached by the author. No attempt has been made to deal with inconsistencies in classification terminology. To organize the review in terms of hypotheses about the occurrence of glaucoma the abstracts of articles read and selected for inclusion were classified and are referred to under headings which ask a hypothetical question.

I. Review of literature

An early question in an epidemiologic appraisal is, what is the pattern of occurrence of the disease over a period of time—is it increasing? decreasing? or not changing? Striking changes aid in recognition of the problem, and suggest certain lines of investigation (for example, lung cancer).

A. Is the incidence of glaucoma changing?

Kurland's[13] survey in Rochester, Minnesota, provides the only figures we know of on the frequency of glaucoma in the United States (table 1). For glaucoma, any evidence of change in the amount of the disease is both scanty and inclusive. Weinstein[14] cites several references which indicate an increase in the number of patients with glaucoma. These examples are based on changes in the proportion of glaucoma patients to total blind or in relation to the number of other patients. In England, Sorsby's[15-17] analyses of data on the registered blind showed the proportion of persons blind from glaucoma to be essentially unchanged for three periods, 1933-43, 1948-50, 1951-54, with 13.4 percent, 14.0 percent, and 13.6 percent respectively. On the other hand, the proportion of the aged in England's general population is increasing, and the percentage of newly registered blind from all causes aged 70 years and over has continued to rise sharply since 1937 when the figure was first available. Chang[18] found 1.75 percent patients with primary glaucoma among 13,807 new patients seen in 1948 in the out-patient clinic of the Department of Ophthalmology in Tung Jen Hospital in Peking, which he notes is higher than the 1.11 percent reported by Pillat[19] in 1932 in the Peking Union Medical College. Maziny[20] examined figures on the cases of primary glaucoma among patients at the Egyptian ophthalmic hospitals from 1916-1935. With the one exception of 1930, he found from 1921 through 1935 a steady drop each year in the percent of cases. This drop, he explains, results from the increase in the number of ophthalmic units in Egypt and the tremendous increase over the years in their use by the people even for relatively minor eye complaints which in earlier years would have been ignored. This attention to less serious ailments thus influences the percentage distribution of the more serious conditions. In 1921, 127,223 patients were examined, 2,254

TABLE 1

Glaucoma: Prevalence and prevalence rates for population of Rochester,* Minnesota December 31, 1954, by Sex and Age

Age (yr.)	Population*		Chronic Simple glaucoma				All Types of Glaucoma					
			Male		Female		Male		Female		Both Sexes	
	Male	Female	Number	Rate/1,000 population	Number	Rate/1,000 population	Number	Rate/1,000 population	Number	Rate/1,000 population	Number	Rate/1,000 population
0–24	4,937	6,454	0		0		2	0.4	0		2	0.2
25–44	4,000	4,899	0		0		3	0.8	0		3	0.3
45–54	1,560	2,056	0		1	0.5	0		1	0.5	1	0.3
55–64	1,338	1,625	6	4.5	3	1.8	6	4.5	4	2.5	10	3.4
65–74	781	1,125	1	1.3	6	5.3	3	3.8	9	8.0	12	6.3
75–84	330	519	0		6	11.6	0		9	17.3	9	10.6
85 plus	63	124	0		3	24.2	1	15.9	4	32.3	5	26.7
Total	13,009	16,802	7	0.5	19	1.1	15	1.2	27	1.6	42	1.4

* April, 1950, census.

(1.77 percent) of whom were primary glaucoma cases; in 1935, 1,049,584 were examined, 7,680 (0.73 percent) of these having primary glaucoma.

B. WHAT IS THE GEOGRAPHIC DISTRIBUTION?

Does the geographic distribution of the disease provide any leads to causation? Again, for lung cancer and coronary heart disease, geographic differences have been noted. For glaucoma, the data reviewed so far provide limited and uncertain evidence. We may look first at the "mortality data" for glaucoma, that is, the blind persons. A recent report by the WHO presents the results of recent estimates and census counts of the prevalence of blindness in various parts of the world.[21] There is a considerable range in blindness rates per 100,000 population (from 47 in the Netherlands to 549 in Nigeria). Any interpretation of these differences must take into account the variety of methods of enumeration, definitions of blindness, and different causes of blindness. Even among countries of comparable living standards the range in blindness rates is wide (for example, 47 for the Netherlands to 179 for England and Wales). Unfortunately, the proportion of blindness due to glaucoma is not included in this report. Hence the present use of international statistics on blindness is similar to studying, for example, the geographic distribution of deaths from coronary heart disease by using crude death rates—not a very useful device.

Estimates of the proportion of blindness caused by glaucoma have been made in several countries, for different time periods, with different types of data, and using different definitions of blindness.[15, 22-27]

These range from a high of 52 percent of blindness in Iceland, 10 to 25 percent in several other areas (England, United States, California), to only five percent in Norway. A closer examination of these reports will indicate the inherent limitations of such data for making useful comparisons. Bjornsson[22] was able to study 143 blind persons of a group of 434 listed as blind in Iceland. He found that 75 (52.4 percent of the 143) were blinded by glaucoma, certainly a very high proportion. These were almost exclusively cases of primary "chronic simple wide-angle" glaucoma, "acute" glaucoma being very rare in that country. The author points out that blindness from senile cataract is not common in Iceland, and that many of the infectious diseases producing blindness in other countries are unknown as causes of blindness in his country. These factors influence the percentage distribution of the other causes.

In this country, the Social Security Administration's[25] analysis of the causes of blindness among nearly 21,000 recipients under the aid to the blind program in 20 states during 1940-41 found that 10.5 percent were blind because of glaucoma. The percentages for the individual states varied widely, from 3.4 percent in South Dakota to 15.0 percent in Maryland. More recently the California State Health Department[1] found that glaucoma was the cause of blindness for 13.7 percent of the 12,500 recipients under the aid to the blind program in that state in December, 1954. Reporting on the register maintained by the Delaware Commission for the Blind, Howland[26] states that 24.3 percent of the reported cases were caused by glaucoma. Of a total of 390 cases on the register (circa, 1949), 95 were glaucoma victims. As it is generally acknowledged that much blindness goes unreported in states maintaining registers, one cannot say whether this distribution is typical of all the blind in Delaware.

Holst[24] provides statistics on the blind in Norway in 1948. Of a total of 3,181 blind, he found 145 cases of glaucoma "simplex" and five cases of "inflammatory" glaucoma, or 4.7 percent of the total. The sources of the author's data apparently are pensions to the blind and organizations for the blind. He notes that his figures on the elderly blind in Norway may be incomplete, because after

the age of 70 years the blind come under the regular old age pension plan. Some of these elderly blind might not be known to organizations for the blind and would thus be omitted from Holst's figures.

Moving along the spectrum of disease from blindness at one end toward unrecognized disease at the other, what about the occurrence of clinical disease in the general population? Lehrfeld and Reber[27] reviewed various reports on this subject and found the following ranges:

	Percent	Reports
Asia	0.86 to 2.60	10
Africa	1.75 to 2.00	2
Europe	0.40 to 2.40	12
Europe	1.02 to 1.24	3

(Compiled by Nelander)

Another measure of the prevalence of glaucoma is the proportion found in hospital or clinic admissions or among patients consulting eye physicians. The literature contains a variety of such figures, and here, too, there are undoubtedly serious limitations on the data for comparative purposes. Among 242,533 admissions to the Wills Eye Hospital between 1925 and 1936, Lehrfeld and Reber[27] found 1,876 (0.78 percent) with glaucoma. Posner and Schlossman,[28] noting that the literature shows estimates ranging from 0.5 percent to two percent with glaucoma of all patients consulting ophthalmologists or clinics, found 3.1 percent with primary glaucoma out of 12,000 case histories of private patients. In the Philippines, de Ocampo[29] notes that of 2,012 eye cases seen in the Eye Clinic of St. Luke's Hospital during a 14-month period, 80 (four percent) had glaucoma including both primary and secondary types. Phelps[30] reviewed records of the patients he had seen during one year. Of a total of 720 over the age of 45 years, 37 (five percent) were glaucoma patients. At the University Eye Clinic in Oslo, Norway, the admissions between 1920 and 1939 totaled 24,127. Holst[31] reports that 2,024 of these were glaucoma "simplex" patients, or 8.4 percent.

Finally, what about inapparent disease? Screening surveys are beginning to provide some data on prevalence, suggesting that about two percent of the population over 40 years of age have unrecognized glaucoma. One of the earliest of these screening efforts was the one conducted by the Philadelphia Committee for Prevention of Blindness. Brav and Kirber[3] report that, among 10,000 employees aged 40 to 65 years of large industrial plants which co-operated in the study, 1.53 percent were found with definite or early glaucoma. Because some of the additional borderline cases may be expected to develop glaucoma and because the aged population was not really represented in this study, the authors estimate that the amount of undiscovered glaucoma in the general population over 40 is two percent. A one-day survey in Cleveland during which over 12,000 persons were screened supported this estimate, according to Wolpaw and Sherman.[5] Vaughan, et al.,[32] found a similar proportion of glaucoma among 1,000 patients in a mental hospital in California. Koskenoja and Orma[33] screened 600 geriatric patients over 64 in Helsinki, Finland, and found 28, or 4.6 percent, with primary glaucoma. Of these, 15, or 2.5 percent of the series, were previously undetected cases. Foote and Boyce[4] summarize the findings of several glaucoma screening programs and note that the results have established the value of this method of detecting the disease in its early stages.

C. Is there a seasonal distribution?

A number of observations have indicated that in certain northern hemisphere countries, acute attacks of glaucoma are more frequent during the winter months. Weinstein[14] chartered 573 acute glaucomatous attacks from information contained in the records of patients covering a 30-year period of the First Ophthalmological Clinic in Budapest. The months of January, February, and March were highest with 75, 70, and 67 acute attacks, respectively, and the months of June, July, and August were

lowest with 33, 33, and 34 attacks. In a rather small series of 141 attacks of acute glaucoma, Lehrfeld and Reber[27] found a somewhat similar distribution. Attacks were most numerous in December, January, and March, with 17, 17, and 15, respectively, and the months of June, July, August, and September were lowest with nine, nine, eight, and eight attacks. In a group of Chinese patients with primary glaucoma, Lo[34] observed that the disease began in 44 percent of the 87 eyes with "congestive" glaucoma during August, September, and October, which corresponds to the rainy season in Chengtu. Gerloff[35] analyzed 64 acute glaucoma attacks and found that, if attacks resulting from a known factor—such as the death of a relative—were excluded, the peak of incidence occurred between September and January and again in July. He also observed a correlation between the variations in intraocular pressure and changes in the weather in cases of chronic glaucoma. Sautter and Daubert[36] analyzed the occurrence of attacks of "acute" glaucoma in 64 cases in an effort to determine the influence of the upper atmosphere. They found that the occurrence of the attacks could be reckoned statistically to be influenced by the upglide motion and turbulence processes, while they found a negative correlation for the other atmospheric processes. Weinstein[14] described a study by Luzsa[37] in which he analyzed the monthly and daily distribution of acute attacks from clinic records for a two-year period. These he compared with exact meteorologic records for the same period. In approximately 50 percent of the cases he found a connection between the time of the attack and a break in fronts. Knecht[38] in his study of the influence of weather changes on intraocular pressure noted that a group of clinic patients with elevated tensions distributed on the basis of month, day, and year between 1936 and 1945 appeared to show patterns of correspondence with days of disturbed weather (table 2).

While the seasonal variation in the occurrence of attacks of "acute" glaucoma has been explored for some years, in a recent report from England Lloyd[39] studies the possibility of a variation in occurrence of cases of "simple" glaucoma based on date of diagnosis. Because of the association between the "congestive" glaucoma which occurs in some cases of epidemic dropsy and alkaloid poisoning, the possibility exists that some cases of "simple" glaucoma can be attributed to alkaloid poisoning. If this possibility is correct, Lloyd points out that some glaucoma cases may fall into some kind of epidemiologic grouping. He attempts to test this idea, first by using the month of onset in each case and each eye and, then when this was found to be impossible to determine, by the date of diagnosis in cases which had tonometric readings above 45 mm. Hg. His assumption was that in cases with such high tensions the diagnosis occurred reasonably soon after onset. He draws several charts from data available in Oxford City and vicinity, and in some of these he finds "encouraging groupings." For example, in one chart of 30 Oxford City primary simple cases covering 1945-53, he

TABLE 2

INFLUENCE OF WEATHER ON "CHRONIC SIMPLE GLAUCOMA"
(Totals After Knecht[38])

Years	Number Cases with Tension 10 mm.* or More	Number Cases and Percent Occurring on Days of Weather Disturbance		Number Days Observed	Number and Percent of Those Days which had Disturbed Weather		Difference Between Columns 3 and 6
1936–1945	198	65	34%	395	94	24%	10%

* Scale not indicated.

found a complete absence of cases in 1947 and early 1948 and a six months' gap in the first half of 1950. He found three groupings between August, 1948, and March, 1949, July and November, 1949, and again between July, 1950, and April, 1951. He cites as the best lead to epidemiology that he has found, a chart showing a pattern in a rural area in which four gaps occur in the incidence of "simple" glaucoma and each is followed by a corresponding gap in the incidence of secondary glaucoma occurring some months later. Lloyd does not attempt to draw conclusions from this study, but he does stress the need for developing a much more accurate method of placing the time of onset of each case.

D. What is the age and sex distribution?

What is the age and sex distribution of glaucoma? Data from hospital series and analyses of aid to the blind programs are in agreement that the primary glaucomas are to be found in the older age groups. Hurlin's[25] study of recipients of aid to the blind in 20 states shows the following age distribution for those blinded by glaucoma:

Years	Percent
Under 20	Less than 0.05
20-29	0.5
30-39	1.8
40-49	4.7
50-59	12.9
60-69	24.7
70-79	34.7
80 and over	20.6
Unknown	0.1

On the basis of 1,586 cases of glaucoma, the California State Health Department's[1] recent study of the aid to the blind program in that state shows the following distribution by age of those blind from this cause:

Years	Percent
16-24	0.3
25-34	0.7
35-44	2.0
45-54	6.6
55-64	13.8
65-74	28.3
75-84	35.6
85 and over	12.3

Chang[18] presents a percentage distribution in his study of glaucoma patients seen in an out-patient clinic of a hospital in Peking and compares this with an earlier study by Pillat[19] at Peking Union Medical College (table 3).

Among 145 private and clinic cases of glaucoma in the Philippines, de Ocampo[29] found the largest number of cases—36.6 percent—in the 60 to 69 year age group. Rouse[40] also found the highest number of cases (40, or 32.8 percent) in this age group in his analysis of 122 "chronic simple" glaucoma patients treated at the Eye, Ear, Nose, and Throat Hospital in New Orleans between 1931 and 1936. Among the glaucoma patients at Wills Hospital, Lehrfeld and Reber[27] likewise found that the age group 60 to 69 years contained the largest proportion of glaucoma patients. The age distribution by type of glaucoma is as in Table 4.

Age data available from a Philadelphia screening survey presented by Hankla[41] indicate a similar age distribution. As data from such screening surveys accumulate, age and sex specific rates should be examined for consistency with the case series. The suggestion in Lehrfeld and Reber's

TABLE 3

Chang's[18] percentage distribution of glaucoma patients compared with Pillat's[19]

Age in Years	Below 20	21–30	31–40	41–50	51–60	61–70	71 and over	Total
Number of patients	1	2	9	38	96	80	15	241
Percentage (present series)	0.4	0.8	3.7	15.8	39.9	33.2	6.2	100.0
Percentage (Pillat's series)	1.4	1.4	6.9	15.9	30.0	36.0	7.6	

TABLE 4

AGE DISTRIBUTION BY TYPE OF GLAUCOMA
(Lehrfeld and Reber[27])

Age Group (yr.)	"Congestive"		"Simple"	
	Number	Percent	Number	Percent
40–49	45	11.5	125	12.2
50–59	122	31.1	242	23.6
60–69	142	36.2	383	37.4
70–79	73	18.7	242	23.6
80–89	10	2.5	31	3.2
Total	392	100.0	1,023	100.0

figures that the congestive form of the disease appears more in slightly younger age groups is supported by Miller[42] in his study of 81 "congestive" and 99 "simple" glaucoma patients at the Glaucoma Clinic of London's Institute of Ophthalmology. He found that the average age at diagnosis of the "congestive" cases was 54.2 years and in the "chronic simple" cases it was 59 years. In a report on the first 10 months of operation of the Glaucoma Prevention Clinic of St. Sacrament Hospital in Quebec, Pichette and Audet[43] state the average age of 38 male and 73 female patients admitted to hospital was 48 years. Interested in early detection, they also note that 36 of 103 individuals attending the clinic were diagnosed as preglaucoma and that the average age of this group was 30 years.

As to sex distribution, the literature contains some conflicting statistics with regard to "chronic simple" glaucoma, although most reports seem to support the generally accepted idea that "acute" glaucoma is found more often among females. Miller[42] reports 51 females and 30 males in a group of 81 "congestive" glaucoma patients. In a group of 99 "chronic simple" glaucoma patients from the same clinic, the distribution was 52 males to 47 females. Lehrfeld and Reber's[27] Wills Hospital group of congestive cases contained 54.6 percent women to 45.4 percent men; the chronic simple cases were almost evenly divided, with 50.3 percent females and 49.7 percent males. Rouse's[40] group of 122 "chronic simple" glaucoma patients contained a high proportion of females—78 (64 percent) to 44 (36 percent) males. In the group of 145 cases analyzed by de Ocampo,[29] 57.2 percent were women and 42.8 percent were men. About two thirds of these cases were the congestive type. In Holst's[24] study of the blind in Norway, he found 61 percent males to 39 percent females in 145 persons blinded by glaucoma "simplex." He notes that this sex ratio in glaucoma "simplex" is about the same as that observed elsewhere in Scandinavia, while in countries south of Scandinavia women are often found in greater proportion than men. In Bjornsson's[22] group of 75 persons blinded by glaucoma in Iceland, 45 were male and 30 female. These were almost exclusively victims of primary "chronic simple" glaucoma. Chang[18] in 241 primary glaucoma patients, notes a preponderance of females, 64.3 percent to 35.7 percent males. He states that this preponderance is made even greater because the series of clinic patients from which the glaucoma patients came contained almost twice as many males as females. He shows this in the following table in which he compares his series with the earlier study by Pillat[19]:

SEX	PRESENT SERIES	PILLAT'S SERIES
Male	86/9,076 = 0.95%	0.74%
Female	155/4,684 = 3.31%	2.31%

E. IS THERE SELECTION BY ETHNIC OR RACIAL GROUP?

Does there appear to be selection by some ethnic or racial group? An examination of the literature reveals diverse opinions on this aspect of the glaucoma problem, and in many instances these opinions are not backed by useful supporting data. Sugar[44] does not think that any race is predisposed toward glaucoma, and Duke-Elder[45] shares this view. Analysis of 590 glaucoma cases admitted for operation at Wills Eye Hospital in Philadelphia during 1931-35 inclusive showed that 13.2 percent were Jewish, while Jews comprised 12.2 percent of the general population of Philadelphia.[27] A

study of records of patients admitted to the First Ophthalmological Clinic of the University of Budapest during a 30-year period revealed that 12 percent were Jews and 28 percent of these had glaucoma. Weinstein[14] further states that in 1935, seven percent of the dispensary patients had glaucoma while 22 percent of these were Jewish. However, he presumably is speaking of the dispensary of the hospital with which he is affiliated—the Jewish Hospital in Budapest. Conclusions can not be formed on the basis of such scanty information. Many factors may influence the nature of the clientele of a hospital.

In this connection, Brav[48] states that on the basis of his experience he believes that the proportion of glaucoma among Jews is about the same as among other peoples. He explains that the idea that glaucoma was more prevalent among the Jewish people originated in Vienna, long famous as a center of ophthalmologic practice. The Jews, throughout Europe, either because of their own financial resources or with aid from their communities, were able to go to Vienna for treatment, whereas the non-Jewish people did not do this.

Whether or not Negroes have more glaucoma than Caucasians is another question on which the literature provides some conflicting data. In Rouse's[40] group of 122 "chronic simple" glaucoma patients at the Eye, Ear, Nose, and Throat Hospital in New Orleans, 54.1 percent were white and 45.9 percent were Negro. Over half of all the hospital patients were Negroes. The average age of the colored patients was 47 years, while that of the whites was 57 years. A study by Pfingst[47] reveals a different distribution of races in two hospitals in Louisville, although he, too, found the average age of the primary glaucoma patients (exclusive of congenital cases) was lower in the Negroes, 55.2 years to 61.2 for whites. In the glaucoma clinic of Louisville General Hospital, the patients were classified as in Table 5. Pfingst states that the proportion of Negro to white patients in other clinics at the above hospital is about 1:1. He found distribution at the Veterans Administration Hospital in Louisville to be as in Table 6. In interpreting these figures in the veterans hospital, however, it is important to know that the proportion of Negro to white patients here is about 1:8. Pfingst points out that if the population in the VA hospital were on a 1:1 basis, 87 percent of the primary cases would be Negro.

Two reports on aid to the blind programs show glaucoma as a cause of blindness more frequently in Negroes than in whites. Caution should be used in interpreting these data, however, for socio-economic factors probably influence the ethnic composition of the groups under aid to the blind programs. About 20 percent of the total number of recipients in Hurlin's[25] study were Negroes, but 29 percent of the glaucoma cases were Negroes. Glaucoma was indicated as the cause of blindness in 15.2 percent of the Negro recipients as compared with 9.3 percent of the white recipients of aid. This report points out that this difference cannot be explained by differences in sex or age composition of the two groups, since the sex

TABLE 5

CLASSIFICATION OF PATIENTS IN GLAUCOMA CLINIC OF LOUISVILLE GENERAL HOSPITAL (Pfingst[47])

	White			Negro		
	Male	Female	Total	Male	Female	Total
Primary	9	8	17 (22%)	20	44	64 (78%)
Secondary	4	2	6 (30%)	6	8	14 (70%)
Total	13	10	23 (23%)	26	52	78 (77%)

TABLE 6

PROPORTION OF NEGRO TO WHITE PATIENTS IN VETERANS ADMINISTRATION HOSPITAL IN LOUISVILLE (Pfingst[47])

	White	Negro
Primary	27 (53%)	24 (47%)
Secondary	21 (88%)	3 (12%)
Total	48 (64%)	27 (36%)

ratios are the same and proportionally fewer Negroes are in the older age groups.

The analysis of the aid to the blind program in California[1] indicates that glaucoma was the cause of blindness in 27 percent of the Negro recipients compared with 14 percent of the white. Of the total number of recipients in the study, eight percent were Negroes, but this group accounted for 16 percent of the glaucoma cases.

The literature indicates that a discussion of the proportionate amount of glaucoma in Negroes and whites is likely to bring forth the question of anatomic, physiologic, or other differences in the eyes of the two groups. Citation of a few of the articles may be useful, although it is not within the realm of this review to become enmeshed in anthropologic considerations. McNair[48] reports on a questionnaire he sent to 125 ophthalmologists throughout the United States. The purpose of the questionnaire was to obtain the opinions of eye physicians on the prevalence and treatment of glaucoma in the Negro. In response to one of the questions, three fourths of the ophthalmologists stated that they thought that there were anatomic, physiologic, or pathologic differences between eyes of Negroes and whites. Among the factors cited as being characteristic of the Negro eye were increased pigmentation of the uveal tract, tendency toward scar tissue formation, and a thick Tenon's capsule which flays out early thus making for difficulty in filtering operations. Venable,[49] on the basis of 10 years' experience with Negro glaucoma patients at the Homer G. Phillips Hospital in St. Louis, observes that "chronic simple" glaucoma is more fulminating in the dark-skinned Negro with deeply pigmented iris and that the greater quantity of pigment in the dark iris makes it harder to dilate and constrict. He notes, too, that the Negro has more uveal pigment than most races, but he states that the glaucomatous eye in the Negro is physiologically similar to that of other races.

Scott[50] discusses the eyes of the West African Negroes and notes differences between them and eyes of Europeans. The most obvious difference he found was pigmentation. He also notes that stronger mydriatic drugs were required to dilate the pupils of the West African Negroes. The article contains no specific discussion of glaucoma. Boles-Carenini and his associates[51] made a tonographic study of a group of white persons and Negroes to determine if there are any differences in intraocular pressure, facility of outflow, and production of aqueous humor between normotensive eyes of each group. In the study were 107 white persons and 97 Negroes, all between 40 and 92, and all without known eye disease. The authors summarized their findings: "The eyes of persons of the white and Negro races differ anatomically but the dynamics of the aqueous humor are equal in both. Therefore, it seems impossible to maintain the assumption that there is a predilection of Negro eyes for glaucoma."

F. ARE THERE IMPORTANT SOCIAL OR ENVIRONMENTAL FACTORS INVOLVED?

In present day chronic disease epidemiology, investigation of social or environmental factors is assuming increasing importance. It would seem reasonable to inquire into the possible association of these factors with the occurrence of glaucoma. Our review of the literature has uncovered little evidence that attention has been paid to these factors in studying glaucoma. A study by Schmerl and Steinberg[52] perhaps has some indirect implications. They state that it is generally ac-

cepted that a number of different stimuli and conditions may either increase or decrease intraocular pressure. Because the populace is exposed to multiple and various stimuli in the environment, they decided to administer stimuli successively and to evaluate the effects on intraocular pressure. The experiments were conducted on nine rabbits. The stimuli used included: (1) exposure to light (four hours of broad daylight with a 300-watt bulb placed 50 cm. from the cage); (2) exposure to odor of citronellol for 15 minutes; (3) distilled water dropped into eyes every few minutes until 12 to 15 drops were given; (4) spinal fluid in 1.0 cc. or larger doses and prepared to contain hyperpiesin injected into vein. These stimuli were applied separately and in various combinations. Each alone increased intraocular pressure by two to six mm. Hg. When several stimuli were applied successively, considerable increases of tension were noted, up to as high as 15 mm. Hg when all four were used successively. The authors noted that when the increase of intraocular pressure reached 10 mm. Hg in the rabbits, manifestations resembling acute glaucoma appeared in these animals.

Best[53] presents data from the 1920 census which show the percentage distribution of blind by cause according to previous occupation. The Bureau of the Census no longer collects information on blindness during the taking of the census, because it feels that this method of determining the extent of blindness is quite unsatisfactory. However, these 1920 data may be of some interest, providing there is an awareness that there are shortcomings in the method by which they were collected. The percentages in Table 7 represent the males blinded by glaucoma of the total males blind in each "previous occupation."

Table 8 is a similar distribution for females.

Bonavolonta[54] studied a total of 1,020 cases of glaucoma among 139,900 patients observed at the eye clinic of the University of Naples from 1936 to 1947. He noted the frequency of the various types of glaucoma, and among other factors the relationship of age, sex, heredity, season of the year, and emotional factors. Comparisons between the incidence during the years of war, as well as that before and after the war, suggest the prominent role played by emotional, social, and environmental factors in determining

TABLE 7

CLASSIFICATION OF MALES BLINDED BY GLAUCOMA AS TO PREVIOUS OCCUPATION (Best[53])

Previous Occupation	Percent Males Blind from Glaucoma of All Males Blind in Each Occupation
Total	5.5
Farmers	4.3
Laborers (building and general)	3.6
Carpenters	5.4
Wholesale and retail dealers	14.0
Professional service	12.2
Mine operatives (not coal)	1.1
Agricultural laborers	1.6
Railroad workers	4.5
Chauffeurs and teamsters	4.5
Blacksmiths and forgemen	4.1
Mechanics	7.7
Soldiers and sailors	1.6
Coal mine operatives	2.1
Machinists and toolmakers	9.0
Clerks and salesmen	13.0
Cooks and servants	5.1
Painters	9.7
Brick and stone masons	6.2
Clerks and stenographers	10.8
Engineers and cranemen	4.4
Iron and steel operatives	2.4
Firemen	2.8
Manufacturers and managers	14.6

TABLE 8

CLASSIFICATION OF FEMALES BLINDED BY GLAUCOMA AS TO PREVIOUS OCCUPATION (Best[53])

Previous Occupation	Percent Females Blind from Glaucoma of All Females Blind in Each Occupation
Total	10.8
Farmers	7.5
Waitresses and servants	7.5
Dressmakers and seamstresses	14.6
Laundry workers	3.6
Teachers	20.1
Cooks	4.5
Agricultural laborers	4.8

the onset of a crisis when local and general predisposing factors are present.

G. What is the influence of heredity on occurrence?

Does heredity influence the occurrence of glaucoma? The matter of an increased expectancy in families of persons with glaucoma has received much attention in the literature. Studies reported by Westerlund[55] seem to support the conclusion that the relatives of glaucoma patients constitute a group with a high prevalence of unsuspected glaucoma. Kellerman and Posner[56] studied 199 patients at Manhattan Eye, Ear, and Throat Hospital's glaucoma clinic and obtained a positive family history of glaucoma in 13.5 percent of this group. Upon examining 192 of the patients' relatives, the authors found eight (4.2 percent) with definite primary glaucoma all of the "chronic simple" type and an additional 11 (5.7 percent) which were classed as borderline cases. They also compared the chamber angles of some of the relatives of the "chronic simple" glaucoma patients with the angles of some of relatives of the "acute congestive" glaucoma patients. Table 9 presents their findings. They state that if the suggestion in the above findings that angle width may be an inherited anatomic feature is borne out in larger samples "this observation will strengthen the concept that chronic simple glaucoma and narrow-angle glaucoma are separate diseases, both clinically and genetically."

TABLE 9

Influence of heredity on occurrence of glaucoma
(Kellerman and Posner[56])

	Number	Percent
Eyes examined of relatives of "chronic simple" glaucoma patients	181	
Eyes with narrow angles in these relatives	12	7.0
Eyes examined of relatives of "acute congestive" glaucoma patients	48	
Eyes with narrow angles in these relatives	12	25.0

Probert[57] studied records of a total of 832 cases which represented all the glaucoma patients in Ontario registered with the Canadian National Institute for the Blind between 1918 and 1949. Of these, 571 were considered primary glaucoma. He found 102 (17.8 percent) with an hereditary history, belonging to 85 different families. The glaucoma type was determined in 80 pedigrees as follows:

"Chronic congestive" glaucoma	55 (69%)
Glaucoma "simplex"	19 (24%)
"Acute congestive" glaucoma	6 (7%)

On the basis of his study, Probert states that glaucoma may be inherited as a dominant or a recessive trait.

Reporting on 373 cases of primary glaucoma seen in private practice, Posner and Schlossman[28, 58] found 14 percent (51 cases) which had a relative with the condition. In 30 families they found a total of 99 cases. In their analysis they noted that all types of glaucoma were represented in the hereditary group.

Among 81 cases of "congestive" glaucoma, Miller[42] found eight with a family history of the disease, and in 99 cases of the "simple" type he found 10 with a family history. He does not feel that the finding of a family history in 10 percent of these cases is very accurate, however, since many patients have little knowledge of their relatives.

H. What is the role of emotions?

Emotional crises have long been considered associated with some episodes of "congestive" glaucoma. The 19th-century ophthalmologist, Laqueur,[59] writing of his own case of glaucoma, noted that he soon recognized that psychic factors influenced the onset of his attacks. Anger, anxiety, humiliation, and pleasurable excitement aroused by stirring music were among these factors.

Schoenberg[60, 61] presents a number of case histories in which anxiety states have precipitated attacks of primary glaucoma. He points out that states of emotion are evolved in the same regions of the brain where the autonomic nervous system is located, that the adrenal and pituitary glands are functionally linked with the autonomic nervous system and are involved in the mechanism of emotions, and that the effects of emotions are transmitted to the rest of the body by the autonomic system and the hormones of the pituitary and adrenal glands. In the glaucomatous eye, the sympathetic and parasympathetic parts of the autonomic nervous system are out of balance. He emphasizes the importance of determining the patient's psychic problems.

Lowenstein and Schoenberg,[62] by means of pupillography, found that all cases of primary "simple" glaucoma showed constant characteristics in the pupillary reflex to light indicative of a central sympathetic condition. The authors conclude that, while lesions of the central nervous system appear to be important in the genesis of "simple" glaucoma, they are not certain whether these are primary or secondary to other etiologic factors such as nutritional deficiency or toxicosis.

Harrington[63, 64] points out that evidence is accumulating which shows a relationship between intraocular vascular circulation, the secretion of intraocular fluid, the level of intraocular pressure, and their control by the autonomic nervous system. Four case histories in which increased intraocular pressure was traceable to emotional upsets are summarized by Sykes,[65] who agrees with Schoenberg's concept of an imbalance between the two parts of the autonomic nervous system.

Ripley and Wolff[66] made an intensive study of 18 patients with primary glaucoma. They report that all had a history of difficulty in personality adjustment, manifested in mood fluctuations, excessive anxiety, and hypochrondric tendencies. Compulsive traits were common, all had unsatisfactory relationships with one or both parents, and had feelings of insecurity. They found mature interpersonal relationships difficult. All had a history of anxiety, anger, or depression connected with a frustrating life situation at onset of glaucoma. They usually reacted to problems with aggressive activity inappropriate to a satisfactory solution. They sometimes expressed emotion on trivial matters while major problems were evaded and repressed. The authors state that they found these same features of psychobiologic adjustment in patients with essential hypertension.

In a study consisting of ophthalmologic and psychiatric examinations of nine primary glaucoma patients at different stages in the development of the condition, Ourgaud, Cain, and Berard[67] believe that there may be such a thing as psychosomatic glaucoma. Weinstein[68] feels that an abnormal function of the cortex is indicated by the personality traits of glaucoma patients and their tendency toward acute attacks following psychic excitement. He believes that proof of the cortical regulation of ocular tension is found in the fact that intraocular pressure falls after a leukotomy operation. He bases this belief on six of his cases, five of whom had low tensions two or three years after leukotomy. He does not state what the tension measurements were before the operations.

Weinstein describes an experiment by the Russian ophthalmologists, Archangelsky and Kravkov, which indicated that intraocular pressure could be decreased by conditioned reflex. This involved a group of glaucoma patients who responded well to pilocarpine therapy. The dropping of this drug into their eyes was synchronized with the ticking of a metronome. After a time, pure distilled water was substituted for the drug. The intraocular pressure continued to decrease upon the administration of the water simultaneously with the ticking metronome. Weinstein points out that, according

to Pavlov, the conditioned reflex is produced within the cortex. He cites the work of others which indicates that the anterior part of the hypothalamus exerts a tonic regulative influence on the cortex while the posterior part inhibits it.

Several efforts have been made to determine the psychologic nature of groups of glaucoma patients. In Miller's[42] study of 180 cases at the London Institute of Ophthalmology, the psychologic backgrounds of the patients were judged on the basis of interviews by social workers. This determination was as follows:

	Congestive	Simple
Anxious	48	41
Overconscientious	11	7
Depressed	2	1
Aggressive	3	3
No obvious pattern	17	47
	81	99

Hibbeler[69] administered the Minnesota Multiphasic Personality Inventory to white primary glaucoma patients, 15 males and 12 females. The group included both "chronic simple" and "acute" cases. She found that over two thirds of the patients showed marked deviations on one or more of the personality scales in contrast with five percent of the original normative group showing such marked deviations. The males tended toward "depression" and "hysteria," the females toward "paranoia" and "schizophrenia." These trends were substantiated by all social information available on the patients.

Fifty primary glaucoma patients—37 with "chronic simple" and 13 with "acute"—were given the Szondi test by Salzmann[70] to determine their "drive nature" and "drive dynamics." According to the author, the results indicate glaucoma patients lack love and tenderness and have personal contact difficulties. "Ego-psychologically" they belong to these groups: the conversion-hysterical; paroxysmal; the normally adaptive; and the destructive, possibly paranoid. This is intepreted as supporting the theory that glaucoma patients unconsciously wish to lose sight of the world through destruction of the organ of sight. The author states that glaucoma patients contain in themselves a paroxysmal epileptiform structure and fall ill through conversion. On the basis of a genealogic analysis of blood relatives by marriage, Salzmann believes that glaucoma patients probably belong to the epileptiform, paroxysmal genetic circle. If additional research confirms these findings, the author thinks that glaucoma may be regarded as epilepsy of the eye or as an epileptic equivalent.

I. Is glaucoma associated with a particular type of refractive error?

The literature contains a number of articles in which data on the refractive errors of glaucoma patients are presented. The most significant findings are those which show comparisons with refraction in the general population. Unless such comparisons are made, the information can be misinterpreted as indicating that hyperopic eyes are more susceptible to glaucoma. Such misinterpretations have been made in the past and have not been questioned because, as Blake[71] points out, hyperopes with their small corneas and shallow anterior chambers, logically would seem predisposed to glaucoma. Posner and Schlossmann[28] compare refractive errors of 538 eyes of glaucoma patients seen in private practice with the refractive status of the general population between 30 and 40 years of age as determined by Jackson. They conclude that a myope appears to be as susceptible to glaucoma as a hyperope. Their findings are given in Table 10.

Holst[31] analyzed records of 1,417 eyes with glaucoma seen at the University Eye Clinic in Oslo during the period from 1928 to 1939. Refraction was measured before operation by Donders' subjective method. He compared his findings with the distribution of refractive errors in a normal group over 30 years of age as found by Herrnheiser:

TABLE 10

TYPES OF REFRACTIVE ERROR ASSOCIATED WITH GLAUCOMA
(Posner and Schlossman[28])

Refractive Errors in Diopters	"Congestive"		"Chronic Simple"		Total Glaucoma		Normal (Jackson)	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Emmetropia (−0.50 to +0.50)	44	23.3	114	27.8	141	26.2	—	12.4
Hyperopia (above +0.50)	114	60.3	169	48.4	283	52.6	—	70.4
Myopia (above −0.50)	31	16.4	83	23.8	114	21.2	—	17.2

	GLAUCOMA PATIENTS (Holst) %	NORMAL GROUP (Herrnheiser) %
Hyperopia	25.6	55.0
Emmetropia	50.7	30.0
Myopia	19.1	15.0
Astigmatism	4.6	

Holst points out that his records do not indicate what the refraction was before the manifestation of the signs of glaucoma and that he is unable to determine from his material whether some of his patients became myopic from pilocarpine medication and/or progression of the disease. Holst makes a tentative conclusion that "hypermetropia plays a considerably more important part in congestive glaucoma than in glaucoma simplex, while a combination of myopia and congestive glaucoma is more rare than that of myopia and glaucoma simplex." In this latter respect, Lagrange and Gilbert, as cited by Blake,[71] make a similar observation. Among their cases of glaucoma, they found one third of the glaucoma "simplex" patients with myopia but only one tenth of the "acute congestive" glaucoma patients with myopia.

Lehrfeld and Reber[27] observe in reviewing the literature on this subject that most authors agree that the glaucomatous eye is hyperopic. In their own series, they analyzed 309 cases for which they had information on refractive status:

	"Simple"		"Congestive"	
	No.	%	No.	%
Hyperopia	35	24.3	68	41.2
Emmetropia	46	31.9	49	29.7
Myopia	20	13.9	24	14.5
Mixed	43	29.9	24	14.5
	144		165	

In his comparison of "congestive" and "simple" glaucoma cases, Miller[42] found the distribution of refractive errors as shown in Table 11.

Weinstein[14] had refraction information on 1,459 of the glaucoma cases from the records of the patients at the First Ophthalmological Clinic in Budapest. Of these, 23 percent were emmetropic, 62 percent hypermetropic, and 15 percent myopic. He calls attention to Hruby's[72] compilation of literature as to the division of refraction among the general population (table 12). He stresses the point that there appear to be fewer myopic persons with glaucoma because in the general population myopes are in the minority.

J. IS THERE A RELATIONSHIP BETWEEN BODY BUILD AND GLAUCOMA?

Some attention has been paid to the possible relationship between glaucoma and general body constitution. One of the early studies was made by Rossi,[73] who, after making anthropologic measurements of a number of glaucoma patients, concluded that the brachycephalic alpine race is especially prone to glaucoma. Both Blake[71] and Weinstein[14] note the work of Nemeth,[74] who found that glaucoma in pyknotics is more likely to be of the "inflammatory" type while in the asthenics it tends more often to be glaucoma "simplex." In a more recent study, Funder[75] compared 300 glaucoma patients (100 with "acute" glaucoma and 200 with "chronic simple") with a control group of 475 without the disease. Over 50 percent in both series of glaucoma patients were of

TABLE 11

DISTRIBUTION OF REFRACTIVE ERRORS IN GLAUCOMA PATIENTS (Miller[42])

	Hypermetropic	Myopic	Emmetropic
"Congestive"			5
Up to 1.0 D.	22	9	
Up to 2.0 D.	21	1	
Up to 3.0 D.	10	1	
Over 3.0 D.	10	2	
	63 (77.7%)	13 (16.0%)	5 (6.2%)
"Simple"			12
Up to 1.0 D.	26	17	
Up to 2.0 D.	15	4	
Up to 3.0 D.	9	5	
Over 3.0 D.	7	4	
	57 (57.6%)	30 (30.3%)	12 (12.1%)

the pyknotic type, whereas only 27.4 percent of the normal group could be classified this way. On the basis of his study, the author concludes that this somatic type apparently has a stronger disposition to develop glaucoma than other types.

K. IS THERE A CONNECTION WITH NUTRITION OR WITH ALLERGEN OR TOXIN SENSITIVITY?

In an effort to determine the effect of diet upon the physiology of glaucoma, Maslansky[76] studied the diet records of 62 glaucoma patients at the glaucoma clinic of the Institute of Ophthalmology, Presbyterian Hospital, New York City. The group consisted of 17 males and 45 females, all but three of whom were over 40 years of age. Physically, most of them could be described as thin. All had low or marginal incomes. The diet records were calculated for calories and eight nutrients and then compared with a National Research Council's recommended allowance and with Ohlson's findings on recall diets. No gross deficiency could be correlated with glaucoma, although in few of the diets was there an adequate intake of all factors. Maslansky states that there is need for additional study of dietary factors in which many groups will be included and in which one factor at a time can be controlled.

TABLE 12

REPORTED DIVISION OF REFRACTION AMONG THE GENERAL POPULATION (HRUBY[72])

Author	Myope	Emmetrope	Hypermetrope
Herrnheiser	13%	31%	56%
Betsch	13%	56%	31%
Kronfeld and Devney	14.5%	15.8%	69.7%

A number of provocative articles have appeared which suggest allergens or toxins as causative agents in at least some cases of glaucoma. In his discussion of "acute congestive" glaucoma, Duggan[77] states that the disease can be considered an allergy since allergy is a manifestation of changes in the permeability of membranes or of smooth muscle spasm. "All substances, whether of chemical, nervous, or endocrine origin," the author points out, "which, by virtue of their presence or their absence, alter capillary permeability or cause arteriolar spasm are possible etiologic agents. Since oxygen is most important for maintaining normal capillary permeability, and since ordinarily the blood contains sufficient oxygen, it is apparent that acute glaucoma is a manifestation of localized capillary and tissue anoxia. . . . Which cases of acute glaucoma are due to protein allergy (histamine resulting from antigen-antibody reaction) and which to physical allergy (histamine formed by ac-

tion of cold on the skin) or to overaction of the sympathetic nervous system cannot always be determined."

Hansen[78] thinks that glaucoma described as caused by allergy is usually in cases of angioneurotic edema or Quincke's edema and should be classed as secondary glaucoma. Wiseman and Moore[79] describe a case of recurrent "simple congestive" glaucoma which was becoming progressively worse until legumes and oranges were removed from the diet. Both eye pain and gastrointestinal distress disappeared. Further experimentation showed that these food items brought on attacks when they were placed back in the diet, and when they were removed again the attacks once more subsided. The authors surmise that certain blood vessels of the eye can act as an "allergic shock organ" to produce an increase in ocular tension. They agree that there is a need for more investigation of the food allergy aspect of the glaucoma riddle.

Using the pulse-diet method of Coca to determine specific allergies, Berens, Girard, and Cummings[80] removed indicated allergens from the diets of three glaucoma patients. Definite improvement was noted in all three cases. In one notable case, the visual acuity in the right eye improved from 20/200 to 20/100 within one year and a definite improvement in the fields was found after beginning the allergen-free diet. Interestingly, the chronic constipation which had afflicted all three patients disappeared after beginning the diet. The authors caution against drawing definite conclusions from their findings because of the many uncontrollable factors in the treatment of glaucoma. They believe further investigation is indicated. As Wiseman and Moore[79] point out in their discussion of this article by Berens, et al., apparently no attempt was made to determine if the glaucoma would be reactivated by introducing the offending foods once again into the diets of these patients.

Nicotine as a causative agent in various diseases has long been a topic of discussion and more recently has been subjected to rather intensive investigation. In glaucoma, however, the literature we have examined seems to confine itself to the effect of nicotine on the eye which already has the disease. Sanna[81] indicates that it is generally agreed that nicotine, even the amount in one cigarette, raises intraocular pressure. Apparently, the higher the intraocular pressure in glaucomatous eyes, the more pronounced and persistent are the effects of nicotine on the pressure and on enlargement of the angioscotoma. Thus, he feels that this drug may aggravate glaucoma symptoms in patients with the disease.

Kanda and So[82] studied 22 opium habitues to determine whether their usually contracted pupils resulted in below normal intraocular pressure and also to determine whether the similar vagotonic condition in which both glaucoma patients and opium addicts are supposed to be makes this group more liable to glaucoma. The group was composed of "Formosan Chinamen" of ages ranging from 33 to 62 years with an average age of 47.5 years. They were hospitalized for two months during the study. The authors found that, in spite of the contracted pupils of the habitues, the intraocular pressure was found to be normal on the average. Furthermore, since the pressure, in general, was found to be normal, their vagotonic condition did not seem to make them more likely to acquire glaucoma. Withdrawal of opium and treatment of the habit did not seem to influence the intraocular pressure readings.

The subject of epidemic dropsy glaucoma in India is often encountered in the literature, but agreement on its significance is not often found. It is Agarwal's[83] experience that this type of glaucoma is a complication in from three to four percent of those who get epidemic dropsy and that 90 percent of these glaucoma cases are among India's middle class and rich. He finds it most common in the age group 18 to 35 years. At the

time of his writing in 1942, he noted that some supposed the cause to be in a toxin generated from rice or mustard oil. Some, as Marquez,[84] believed it should be considered a secondary glaucoma since it is a concomitant of epidemic dropsy. Regardless of its classification, however, some intriguing etiologic implications have been found in the literature, climaxed by Hakim's[85] article in 1954.

Hakim tells us that epidemics of dropsy and glaucoma in India were traced in 1926 to cooking oils which contained the seed-oil from the Argemone mexicana, or prickly yellow poppy. It was not until 1948 that the alkaloid, sanguinarine, was isolated from the oil. Argemone oil, according to Hakim, is the only known substance capable of causing glaucoma in humans. This suggestion of a toxic etiology in epidemic dropsy glaucoma caused Kirwan[86, 87] to speculate on the possibility of a similar toxic etiology in primary glaucoma in other parts of the world. Hakim describes his own experiments on 150 rabbits which, he states, "have shown for the first time that both argemone oil and sanguinarine, in very minute doses, cause acute and chronic rises in tension, histopathologic changes at the filteration angle, and retinal degeneration." Certain other closely related alkaloids, some common papaver oils, and extracts from some papaver plants also produced a similar rise and changes. He believes that the protective action of proteins in a well-fed population may prevent toxic glaucoma from being widespread. He suggests methods by which the toxin may be transmitted, including such possibilities as animal vectors, milk, eggs, and the contamination of cereals with the toxic weeds. In his experiments, Hakim found that argemone oil and sanguinarine had three fundamental actions: an anti-adrenaline action; histopathologic effects on the cornea, filtration angle, retina, and skin; and effects on tissue fluid balance. He says there is yet to be found a single unifying "biochemical lesion" which may co-ordinate these three actions. He concluded that "chemical, pharmacologic, and ophthalmologic evidence lends support to a theory of the toxic etiology of primary glaucoma in other parts of the world by indirect ingestion of papaverlike substances."

L. Are there clues for epidemiologic investigation in the findings on pathogenesis?

There are wide divergences of opinion about the etiology and the fundamental nature of primary glaucoma. Duke-Elder[88] states that the essential difference between the two extreme views is that in the first the pathology is localized in the eye, while the second insists that in simple glaucoma there is a sick eye in a sick body. In speaking at the glaucoma symposium at the XVII International Congress of Ophthalmology, he commented, however, that the distinction between the two schools of thought on the pathogenesis of glaucoma was discovered to be more apparent than real. Sugar[89] agrees that the mechanism of primary glaucoma cannot be thought of on the basis of conflicting mechanism since both are really involved together in varying ways depending on the type of glaucoma being considered. Shaffer,[91] considering the etiology of primary glaucoma at the Pan-American Congress of Ophthalmology in 1952, reviewed the three main theories and concluded that elements of all three are most likely present: a defect of the regulating mechanism of the central nervous system; a defect in the peripheral neurovascular system; mechanical obstruction to aqueous outflow.

As long ago as 1939, Evans[90] was suggesting lines of inquiry into the underlying causes of glaucoma in terms which pointed to cohesion of theories: (1) causes of primary glaucoma are those of venous and capillary stasis and the condition arises from changes resulting from such a disturbance of local circulation; (2) the symptom complex known as glaucoma includes a number of separate conditions whose only features

in common are those represented by ultimate decompensation of the mechanism provided for excretion of fluid from within the eye; (3) primary glaucoma is a local manifestation of a general disease not merely a hypertonic organ but also a sclerosed and dystrophic organ that shares the trouble with the rest of the body.

Whether either form of primary glaucoma, or both, result from intraocular processes per se, or more generalized processes, or a combination of both, we may here go astray if we become enmeshed in the theories and findings pertaining to pathogenesis. But, perhaps, here too there are questions to be asked, in an epidemiologic sense, that may lead to some useful answers.

M. Is the mortality experience of glaucomatous patients different from nonglaucomatous persons?

In an effort to determine whether the mortality experience of glaucoma patients differs from that of the general population Bennett[92] studied all primary "acute congestive" and "chronic simple" glaucoma cases operated on at Southampton Eye Hospital during a 14-year period. He points out that the idea that glaucoma is a manifestation of some generalized vascular or neurovascular upset, rather than a primary ocular disease, has developed from the frequent association of glaucoma and cardiovascular disease. He hypothesizes that if more cardiovascular disease is found among people with glaucoma, they should show a shorter expectation of life than the average. In his study were 105 "chronic simple" glaucoma patients and 33 with the acute congestive form of the disease. Using life tables for England and Wales for 1953, Bennett compared the relative mortality rates of the glaucoma patients with those of the general population and found no significant difference. The patients surviving resembled in every way the patients who died. He concludes that "this seems to indicate that glaucoma patients do not suffer from any excess of the normal process of aging or of lethal vascular disease."

Brand[93] followed 119 glaucoma patients treated at the eye clinic of the University of Pecs in Hungary between 1930 and 1944 to obtain data on association between glaucoma and vascular damage. The group included cases of absolute, chronic, congestive, and hemorrhagic glaucoma. Forty-four of the 119 had died of the following causes:

Circulatory disturbance of cardiac origin	4
Cerebral hemorrhage	12
Cancer of the internal organs	9
Other causes (pneumonia, ileus, operations, and causes not discussed here or unknown)	19
	44

Five of the remaining 75 had had apoplexy, causing Brand to assume that they were probably dead at the time of the study. The author thus concludes that the deaths from apoplexy can reasonably be placed at 17. Of the 17, eight were males and nine females with age at death ranging from 49 to 79 years. This figure of 17 plus those who died from circulatory disturbances of cardiac origin brings to 21—42.8 percent of the total deaths—those attributable to vascular damage. In nearly half of the patients examined blood pressure was higher than 170 mm. Hg.

This author then compares these apoplexy findings with those from autopsies and concludes that the incidence of apoplexy among glaucoma patients is nearly twice as high as is usually found in aged hypertensives. (Brand bases this conclusion on studies which have shown that in Anglo-Saxons over 50 years of age, apoplexy causes from 2.2 to 10 percent of the deaths. In genuine hypertonic patients various authors put the figure at 14 to 25 percent.)

N. Is morbidity of certain types associated with the presence or absence of glaucoma?

This has been considered, most frequently in relation to chronic conditions. However,

Beckh[94] tested the question of an etiologic relationship of syphilis to primary glaucoma. At the Wilmer Ophthalmological Institute, Johns Hopkins, he observed 365 consecutive primary glaucoma cases admitted between 1925 and 1934 to public wards of the institute. Two controls were used in the study: a group with cataracts, and a study of syphilis in general medical admissions to Johns Hopkins. The incidence of glaucoma patients with syphilis was 23 percent, of cataract patients 18.4 percent, and of general medical admission 30.2 percent. The study failed to present any evidence for the view that primary glaucoma is in any way related to syphilis.

The possible significance of focal infections of nasal membranes and accessory sinuses in glaucoma was studied by Berens and Nilson.[97] Of 53 unselected cases of "chronic simple" glaucoma studied all showed varied indications of sinus infection or nasal pathology. Either unilateral glaucoma or more pronounced glaucoma in one eye than in the other was observed in 37 (70 percent) of these cases. In each of these 37 patients nasal involvement was greater on the same side with more active glaucoma. In no case was there marked nasal pathology on one side with markedly active glaucoma on the other side. In those cases where there was considerable pathology, both ocular and nasal, it was either on the same side or else a unilateral ocular condition associated with a bilateral sinus disease.

Magitot[95] and others have written extensively about the vascular etiology of all forms of glaucoma and the elevation of intraocular pressure as merely a symptom of glaucoma. Sunde[96] examined the possible relationship between "simple" glaucoma and general arterial hypertension and some other cardiovascular diseases. Included in this study were 100 patients with "simple" glaucoma who entered the University Eye Clinic at Rikshospitalet in Oslo during 1949 and 1950. Fifty-five were males and 45 were females. All but four were over 50 years of age. Selection of a control group of 100 patients was made by including the first patient without glaucoma to enter the eye clinic following the glaucoma patient and who was of the same sex and was born in the same decennium as the glaucoma patient. Of the control group, 46 had a diagnosis of cataract, and the balance had various other eye problems. The author compared the systolic and diastolic pressure measurements of both groups and found no important differences between them. His table showing the measurements on the day of arrival at the clinic is reproduced as Table 13.

TABLE 13

BLOOD PRESSURE FINDINGS IN EYE CLINIC PATIENTS
(Magitot[95])

Systolic	Glaucoma		Controls	
Under 140	13	30	23	33
140/145	17		10	
150/155	13	26	8	23
160/165	13		15	
170/175	10	19	12	25
180/185	9		13	
190/195	8	25	3	19
200 and over	17		16	
Systolic blood pressure 200 mm. Hg and over with diastolic blood pressure 100 mm. Hg and over	15		14	

Diastolic	Glaucoma		Controls	
Under 70	0	5	1	6
70	3		2	
75	2		3	
80	19	47	25	51
85	2		8	
90	26		18	
95	7	31	4	25
100	23		18	
105	1		3	
110	5	17	9	18
115	2		1	
Over 115	10		8	

Sunde's study included an examination for several cardiovascular diseases, but here also he found nothing in his comparison which indicated a definite difference in frequency of these diseases between the two groups. General arteriosclerosis was not included, as the heart and blood vessels had not been X rayed in all patients. His find-

TABLE 14

RESULTS OF SUNDE'S EXAMINATION FOR CARDIOVASCULAR DISEASE

	Glaucoma	Control
Number of *patients* with one or more cardiovascular diseases or symptoms of these	17	16
Treated for heart diseases	3	5
Treated for general arterial hypertension	3	4
Treated for apoplexy	2	1
Treated for thrombophlebitis	0	4
Treated for nephritis	1	1
Symptoms for cardiovascular diseases: angina pectoris, dyspnoea, cyanosis or oedema	12	12

ings are summarized in Table 14.

An electrocardiographic examination was made on 48 of the 50 glaucoma patients who joined the study in 1950. This test was not made on the control group, so a comparison is not possible. Among the 48, 25 had a normal electrocardiogram, 11 had a left axis preponderance, one had a right axis preponderance, five had hypertrophy of the left ventricle, and six had definite pathologic findings.

Forty-nine of the 50 glaucoma patients from 1950 were given Bexelius' test for capillary fragility. On the basis of Bexelius' standard of up to four or five petechias being normal, 76 percent (37 patients) were found to have a normal capillary resistance. Sunde points out that in 1947 Munroe, Lazarus, and Bell examined a small group of elderly men in good health and found capillary fragility in 21 percent to 31 percent of them. The author concludes that patients with "simple" glaucoma show no increase of peripheral capillary fragility as compared with normal standards.

A urine examination of both groups found 13 glaucoma patients and 13 patients in the control group with symptoms of a pathologic nature. On the basis of the results in all of these examinations the author concludes that no causative relationship can exist between "simple" glaucoma and general arterial hypertension and the other cardiovascular diseases here examined.

In their study of 97 glaucoma patients, Dienstbier, Balik, and Kafka[98] included an examination of the cardiovascular system. Although they give no specific data on blood pressure, they state that they found vascular hypertension more frequently among their glaucoma patients than in others of the same age using the hypertension table of Robertson and Brucer. Capillaroscopy determinations were made under a Zeiss capillaroscopic microscope. These determinations of the condition of the capillaries are in Table 15.

Posner and Schlossman[28] list the ocular diseases and the general disease conditions found in their group of 373 private patients with primary glaucoma. The other ocular diseases they detected among the glaucoma patients were as follows:

OCULAR DISEASE	No. PATIENTS
Cataract	59
Corneal opacities	16
Diabetic retinopathy	7

TABLE 15

RESULTS IN A STUDY OF THE CONDITION OF THE CAPILLARIES
(Dienstbier, Balik and Kafka[98])

Type of Glaucoma	Vasoneurosis	Transitory Forms	Arteriosclerosis	Normal
"Acute inflammatory"	14	4	5	—
"Chronic simple"	2	1	10	1
"Chronic inflammatory"	16	9	11	1
Secondary	6	1	4	12

Drusen in macular area	7
Retinal arteriosclerosis	6
Hypertensive retinopathy	5
Macular degeneration	5
Others (four or less in each grouping)	28

The following general disease conditions were found in these glaucoma patients:

Condition	No. patients
Essential hypertension	64
Diabetes	31
Arthritis	26
Arteriosclerosis	15
Gall bladder disease	14
Allergy	11
Coronary disease	10
Obesity	8
Asthma	8
Deafness (nerve)	7
Hyperthyroidism	7
Psychoneuroses	7
Others (six or less in each grouping)	51

Another listing of systemic conditions found in glaucoma patients is provided by Lehrfeld and Reber.[37] They point out, however, that data on the general medical condition of a great many of the 1,415 patients in their study are lacking. Following are the systemic conditions and the number of patients with each insofar as the authors were able to secure such information on this group:

	No. patients	
Systemic condition	"congestive"	"simple"
Syphilis	10	9
Arteriosclerosis	13	8
Hypertension	55	45
Diabetes	14	23
Nephritis	5	8
Uremia	1	—
Arthritis	4	5
Focal infection	—	26
Eczema	—	1
Myxedema	—	1
Pernicious anemia	—	1

In addition to more or less specific disease relationships which have been hypothesized, a great deal of research on the pathology of glaucoma has pointed to other areas of investigation. Some of these areas are highly suggestive, but because of their clinical nature are somewhat beyond the present opportunity for epidemiologic study. Some of this clinical research, however, clearly attempts to determine what morbid conditions may be associated with glaucoma. Because this may have some indirect implications for the epidemiologist, it may be profitable to include here a discussion of some of the articles which are indicative of the theories that are being explored.

Schoenberg[99] speculates on the similarity of glaucoma to the deficiency diseases, noting that in the early stages of glaucoma in which the balancing mechanism for maintenance of normal intraocular pressure is out of order, drugs bring about partial or temporary restitution of function by specific action on one or several constituent parts of the neuro-effector unit. The necessity of repeated instillation of these drugs at regular intervals, the need for definite dosage, and the recurrence of hypertension when medication is discontinued beyond a certain time limit, points to a similarity between glaucoma and such diseases as myxedema, cretenism, diabetes, night blindness, pellagra, scurvy, and the like in which a fairly normal function can be re-established by constant and regular replacement therapy; namely, pilocarpine-eserine-acetylcholine and thyroid extract, insulin, vitamins A, B, C, respectively.

The endocrine system has received considerable attention in the search for etiologic factors in this disease. Zondek and Wolfsohn[100] studied 22 cases of primary glaucoma, 16 of whom showed evidence of disturbances in the pituitary-diencephalic system. These were manifested in such disorders as obesity, menstrual troubles, abnormal carbohydrate metabolism, tendency toward water retention, deviations of the basal metabolism rate from normal, decalcification or atrophy of the bony skull (particularly around the sella turcica), congestion of the meningeal vessels, and a rise in blood cholesterol.

Schmerl and Steinberg[101] point out that spinal fluid contains active principles, one of which increases and the other of which reduces intraocular pressure tending to bal-

ance. Exposure of eyes to light or darkness is one of the factors which determines the quantitative secretion of one or the other of the active principles. On the basis of experiments on rabbits and ducks, they postulate that these active principles are secreted by the posterior lobe of the pituitary gland. They conclude it is probable that some forms of glaucoma may be induced by a disorder of secretory mechanisms of the active principles.

Another study on the role of the pituitary was made by Yoshioka,[102] who found in his experiments on a small group of humans that the ocular tension and blood pressure were lowered by the anterior and raised by the posterior pituitary hormone. He concluded that the posterior pituitary hormone plays an important part in ocular hypertension.

Radnot and Csillag[103] examined the folliculine and gonadotropical hormone excretion and found it to be normal in 46 of 48 glaucomatous patients; the results indicated that the quantity of hormones excreted by glaucomatous patients does not differ from that of normal people. Included in the study were 11 mature women, 31 women in climax, and six men. Pathologic quantities were found in only two cases.

In an effort to determine the relationship between edematous changes and various types of glaucoma, Lloyd and Robb-Smith[104] made biopsies on the lids of 32 patients with glaucoma and of 24 cataract patients in the same age range. They found an edematous appearance in about two thirds of the glaucoma cases and in very few of the controls. They tentatively conclude that the results indicate a linkage of this edematous change in the eyelids with glaucoma, especially the moderate and high tension noncongestive type.

In another study aimed at differentiating the various types of glaucoma, Lloyd[105] states that he suspects that a positive lid biopsy finding is a manifestation of a generally disturbed vascular lesion and that the vascular factor in the eye is a similar thing. Positive findings would be proportionately high in the high tension chronic group and low in the true acutes, the cause of the latter type of glaucoma being an anatomic factor. His findings tend to substantiate this: in a group of the high tension chronic congestive glaucomas, 83 percent of the biopsies were positive and 17 percent negative; in a group of the true acute, 12.5 percent were positive and 87.5 percent negative.

In the course of studying bodily disturbances which accompany or are associated with glaucoma, various investigators have turned to blood analyses. Massoud[106] found changes in both the red and white cellular elements of the blood. He noted an increase in the red count and a change in the differential white count with a relative increase in the large mononuclears to as much as 15, 20, or even 30 percent. He reports on 10 cases in which the monocyte count ranged from five to 30 percent. He believes this results not from the local eye condition but from some underlying general pathologic process, possibly caused by certain toxins interfering with the function of the reticuloendothelial system.

An opposite finding, however, is reported by Blake and Leonard,[107] who studied the differential blood counts of 100 consecutive unselected patients. Ninety-four of these patients had monocyte counts which could be considered within the normal range (two to 10 percent). The highest monocyte percentage of the six above normal was 15 percent. The authors conclude that the monocyte count is of no value in the diagnosis of glaucoma. In discussing the discrepancy between their findings and those of Massoud, Blake and Leonard point out that protozoan infections, which are more common in Egypt where Massoud made his study, frequently result in rises in monocyte counts.

The blood cholinesterase values of 61 unselected glaucoma patients were determined in a study by Rados.[108] In 59 of the patients, the values ranged from 40 to 120 cu. mm.,

which he considered normal. He did note, however, that the majority had high normal values, and of the 12 patients with acute glaucoma only two were relatively low, the other 10 being toward the upper limit of normal. The need for caution in interpreting such findings is stressed by Rados, since many conditions may influence blood cholinesterase values. Among these are hyperthyroidism, anemia, carcinomatosis, cachexia, sepsis, subacute bacterial endocarditis, pneumonia, and ulcerative colitis.

Schmelzer[109] reported to the German Ophthalmological Society in 1938 on his findings in a systematic study of the blood of 55 patients with primary glaucoma and a control group of 45 persons with normal intraocular pressure. In the 55 cases of glaucoma, he found increases above normal in the bilirubin content, the blood sugar, and the uric acid content. A marked increase in the cholesterol content was found in 51 of the 55 patients, while only 15 of the 45 control patients were found with a similar increase. Seven of the 55 glaucoma patients gave normal values in the test for xanthoprotein in comparison with 33 normal values among the 45 controls. On the basis of these findings, Schmelzer assumed that there was impairment of the hepatic and renal function in patients with glaucoma, but he did not attempt to conclude how important the impairment was in the production of glaucoma.

Liver function tests, including the Takata-Ara test, the thymol turbidity test of the blood serum, and the urobilin test on the urine, conducted more recently by Godtfredsen[119] on 50 patients with moderate to severe "chronic simple" glaucoma, did not support the implication of Schmelzer's findings that liver lesions might have some etiologic significance in primary glaucoma.

A series of biochemical tests were conducted by Dienstbier, Balik, and Kafka[98] on a group of 97 glaucoma patients, 23 of whom were suffering from the acute inflammatory type, 14 from chronic simple, 37 from chronic inflammatory, and 23 from secondary. In an effort to test Schmelzer's findings, they estimated the cholesterol by means of the photoelectric colorimeter. In this way, the level of the total cholesterol and its esters in the serum was obtained. On the basis of the findings in these 97 patients, the authors were unable to confirm Schmelzer's findings of hypercholesterolemia in the majority of his patients. They note that they found a striking decrease in cholesterol esters among all the types of glaucoma represented in their study. They mention that this decrease might be related to changes in cholinesterase and choline.

The results of other tests gave no evidence that glaucoma leads to an increase in the erythrocyte sedimentation rate nor that there is any connection between kidney disease and glaucoma nor between Wassermann results and glaucoma. The authors also studied the colloidal osmotic pressure of these patients. Using 300 to 400 mm. H_2O as normal, they found a decrease below normal in 33 cases, an increase above normal in 24 cases, and normal findings in 40 cases. They tend to discount a relationship between these findings and glaucoma. "It is quite clear," they state, "that the decrease in COP which sometimes occurs in early glaucoma does not play any important part because an increase which would cause quite an opposite reaction was also occasionally noted." They further point out that in other studies showing decreases in osmotic pressure resulting from hypoproteinemia no mention is made of glaucoma as a complication.

II. An epidemiologic approach to glaucoma

Such a review of the literature as the foregoing begins the exploration of available hypotheses. Critical reading immediately indicates the limitations of many of the studies and the lack of acceptable data supporting the various conclusions that have been reached. Either of two approaches is now in order: a descriptive study to fill gaps in knowledge about the "natural history" of glaucoma as it occurs in a human population;

or, if this is not needed, then progression to a systematic sorting, through planned collection of data, of the most likely hypotheses already available.

Three elements common to all field investigation can be mentioned here with the prospects which suggest themselves in California and which guide our design of studies:

A. Selection of the study population

Epidemiology is always concerned with the relationship of cases to the population from which they come. The approach may be from either direction, that is, definition of a population and investigation of cases therein, or study of a group of cases, attempting to relate them back to a population. In California these prospects suggest themselves: selection of a group of cases for study together with a comparable group of noncases from the same population; study of cases found in a selected population group such as an industry, a union, or a group on pensions; assembling for study all cases of glaucoma for a general population such as a city or county. The final choice is influenced by the type of study to be done and the practicability of assembling population and case data.

B. Selection of cases

Since the ability to record the presence of the condition is all important, a prime question deals with the characteristics of the clinical disease. What is the clinical spectrum from inapparent to terminal stages, how recognizable are these stages and their onsets, what are the criteria for diagnosis, and how accurate are the diagnoses? Chronic diseases in general pose important and difficult problems here.[111] Glaucoma does not appear to be an exception. While our interest is primarily directed toward open-angle glaucoma, it may be desirable in these early exploratory stages to include for study all of the primary and secondary glaucomas.

It may be useful to look at cases in another way, for example, sorting them along the range of clinical appearance. In glaucoma, we have the chance, not often possible, to detect and investigate much of the natural range of disease manifestation: the "inapparent" cases (those discovered early through screening surveys), the "active" cases (those diagnosed and under treatment), and also the "fatal" cases (those blind of glaucoma).

The methods used for data collection are not new or unique. As far as possible, emphasis is laid on recording objective measures—verifiable historical data, general medical findings, results of selected special tests. Subjective data on certain factors are also useful.

C. Developing a study

An outline for epidemiologic investigation of glaucoma might be developed along the following lines:

1. *Purpose.* To determine if any of a number of factors to be systematically observed among glaucoma cases separate them more or less consistently from nonglaucomatous control groups.

2. *Method.* The factors to be studied represent a selection from among the hypotheses available from the literature, a selection based on the practicability of assembling case data.

Several groups of cases are studied together with a comparable group of noncases drawn from the same population. Objective measures might be recorded utilizing a questionnaire or a standard general medical index (for example, Cornell Medical Index); subjective data on certain factors elicited in an interview with each study subject might also be useful.

In addition some comparable information could be obtained from other sources where interview is not possible: research of the records of recipients of blind aid who are deceased, including a check against death registration for information comparable to that obtained by questionnaire; research of medical records of all known glaucoma patients in one county to obtain information

of value for comparison with the study population.

3. *Procedures.*

a. To devise a schedule of questions which reflect the most likely theories of causation.

b. By means of interview to complete the questionnaire or medical index on groups of statistically reliable size. For example:

(1) Two hundred recipients of Aid to the Needy Blind whose blindness is due to glaucoma; and 200 such recipients, matched by age and sex, whose blindness is due to other causes.

(2) Two hundred individuals with a diagnosis of glaucoma and under treatment by physicians; and 200 patients, matched by age and sex, who do not have glaucoma.

(3) Two hundred individuals subjectively asymptomatic for glaucoma but found and diagnosed as a result of mass screening programs; and 200 normal controls, matched by age and sex, from the same projects.

Data thus accumulated, processed, and analyzed for suggestive patterns is a promising and neglected method for systematic inquiry into the causes of glaucoma.

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GONIOTOMY TECHNIQUE IN CONGENITAL GLAUCOMA*

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A. INTRODUCTION

Some time has elapsed since the publication of the classic papers of Otto Barkan which described his technique of performing goniotomy under gonioscopic control.[1] It is the purpose of this paper to re-emphasize and to show by photographs the important steps to be taken in doing goniotomy and the points at which the inexperienced surgeon may have difficulty. The technique is applicable in infantile glaucoma, aniridia, Sturge-Weber syndrome, and neurofibromatosis. It has limited applicability in certain juvenile glaucomas. Included is a method of practicing this surgery on animal eyes.

B. PRESURGICAL EXAMINATION

1. CORNEAL DIAMETER (fig. 1)

By means of a caliper, the horizontal diameter of the corneas should be recorded. In an infant a measurement over 11.0 mm. is suspicious. One should look carefully with the microscope for tears in Descemet's membrane. Such tears are never seen in the enlarged cornea of megalocornea. It is the formation of such a tear that results in

Fig. 1 (Shaffer). Measurement of corneal diameter.

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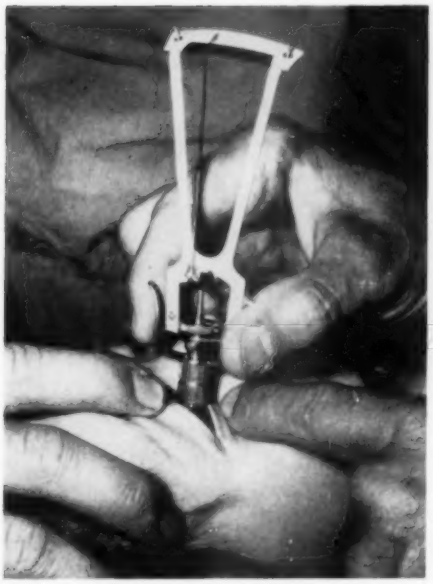

Fig. 2 (Shaffer). Tension with Schiøtz tonometer.

the sudden onset of corneal haziness which attracts the parent's attention and brings the child to the ophthalmologist. A corneal diameter over 14 mm. is a poor prognostic sign. There have been few cures from goniotomy in such advanced cases.

2. Intraocular pressure (fig. 2)

It is important that the patient be at surgical depth anesthesia to avoid false elevations of pressure. Intubation anesthesia is preferable. It is quite possible to find a normal pressure in an eye with glaucoma if little aqueous is being produced at the time. If tonographic facilities are available, a much more reliable diagnosis as well as prognosis can be given.

In the presence of obvious signs of glaucoma with tonographic evidence of decreased outflow, surgery is indicated.[2, 3] If tonographic equipment is not available, surgery is indicated if tension is higher than 2/5.5. If there are no other signs of glaucoma, surgery should be avoided unless tensions are consistently above 2/5.5.

Fig. 3 (Shaffer). Corneal abrasion.

3. Removal of corneal epithelium (fig. 3)

It is often difficult to see through the edematous corneal epithelium of the congenital glaucoma eye. Thorough removal of this epithelium down to Bowman's membrane with a Bard-Parker knife and a No. 15 blade gives marked improvement in visibility. Care should be taken to avoid cutting the limbal vessels as blood getting under the contact lens will obscure the vision. Even if not hazy the epithelium should usually be removed, as it tends to become edematous during gonioscopy if the tension is elevated.

4. Gonioscopy and ophthalmoscopy

The 16-mm. Koeppe diagnostic contact lens without a dimple is placed over the eye. Through it an excellent ophthalmoscopy can be done, avoiding the irregular astigmatism which usually prevents a clear look at the disc.[1] If the pupil has enlarged at all during the anesthesia, the contact lens should be filled with two-percent pilocarpine for the presurgical gonioscopy. The pupil will then be miotic in time for the surgery.

For the gonioscopy one can use standard gonioscopic equipment,[4] or the Zeiss operating microscope. The diagnostic features have been well described elsewhere.[1, 5] There is an anterior insertion of the peripheral iris

but in many eyes it is of such minor degree that it is hard to tell from a normal infant eye. The peripheral iris inserts directly into the trabeculum without a suggestion of an angle recess. In general there is hypoplasia of the superficial iris mesoderm, allowing the pigment arcades to show through prominently. The translucent trabeculum appears somewhat thicker than the usual infant eye. In the presurgical gonioscopy the surgeon should locate the point of iris attachment and Schwalbe's line, as well as the position of blood vessels to be avoided. The actual goniotomy is placed very superficially just below Schwalbe's line in the trabeculum.

Fig. 4 (Shaffer). Position of surgical contact lens and knife.

C. Surgical technique

1. Fixation of the eye

The lateral eyelashes are trimmed. Two Elschnig forceps with locks are firmly applied to the superior and inferior rectus muscles. It is easier to pick up these tendons when the lid and fornix are held out of the way with a muscle hook while the eye is turned with forceps. In my experience a speculum is in the way of the forceps throughout the procedure and therefore is not used. Sutures under the tendons will not slip off but otherwise are inferior to forceps.

2. The surgical contact lens (fig. 4)

The patient's head is turned 45 degrees away from the surgeon so that he can be operating "downhill" thus avoiding bubbles under the Barkan surgical contact lens. The surgeon's left forefinger holds the contact lens against the eye. The Elschnig forceps under that left hand must be rotated out of the way. A drop of saline is placed under the contact lens. The lens is rotated away from the near limbus so that there will be ample room to make the corneal incision.

3. Light and magnification

A Zeiss operating microscope gives excellent magnification and lighting for this surgery and the exact depth of the incision can be controlled by its use (fig. 5). The ×10 magnification seems most satisfactory. When the microscope is set to look at the trabeculum, it is not in good position to control the puncture incision and passage of the knife blade across the anterior chamber. This should be done under direct visualization. Once the blade is beyond the lens, the microscopic view is excellent.

When the patient's cornea is irregularly hazy, the usual ×2.5 loupe is preferable (fig. 6). Illumination is obtained by a hammer lamp held by a second assistant against the surgeon's lateral forehead at the upper lateral frontal bone area. In this way the surgeon is free to move light and visual axis

Fig. 5 (Shaffer). Goniotomy using Zeiss operating microscope.

Fig. 6 (Shaffer). Goniotomy using hammer lamp and loupe.

in any direction to achieve maximal visual clarity. He should stand for this surgery to permit complete mobility. The goniotomy is more easily done and there is less danger of accidental injury to the lens.

4. Positioning of the eye

The assistant must hold the eye so that the plane of the iris is absolutely parallel with the direction in which the knife thrust is to be made. The eye should be lifted upward from the orbit to permit maximum exposure. It should then be rotated so that the incision can be made as far away from the horizontal axis as possible. This permits a second goniotomy to be done from the temporal side if the first one fails (fig. 7).

5. The puncture

The contact lens is held against the cornea but several mm. away from the lateral limbus. The knife is placed against the cornea one to two mm. inside the limbus. The assistant needs to hold the eye against this point to provide support as it is necessary to give a quick thrust to penetrate the cornea with the stubby blade of the goniotomy knife. The blade must be carried rapidly across the anterior chamber to the far side of the pupil to plug the incision by the increasing taper of the handle, thus avoiding aqueous loss. If the Zeiss operating microscope is being used, this maneuver

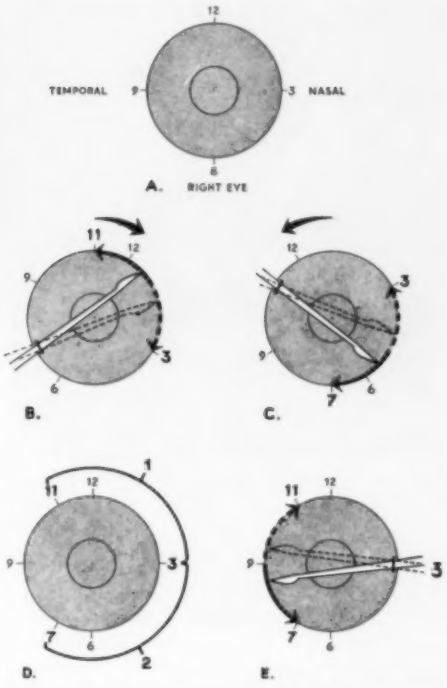

Fig. 7 (Shaffer). Diagram for positioning of eye and goniotomy incision.

should be carried out under direct vision. There is now plenty of time to position the blade exactly against the trabeculum, looking either through the microscope or a binocular loupe.

6. The goniotomy (fig. 8)

The knife tip should engage the trabeculum just below Schwalbe's line and should barely enter the trabeculum. At least the back four fifths of the blade must remain visible to avoid a scleral incision which results in scarring or accidental goniopuncture. It is often necessary to rotate the knife handle around its axis to get the blade far enough into the angle without producing a marked dimple in the cornea at the point of the puncture. This dimple allows a bubble to enter under the contact lens if the lens is not rotated away from the puncture site. With the knife tip engaged, the con-

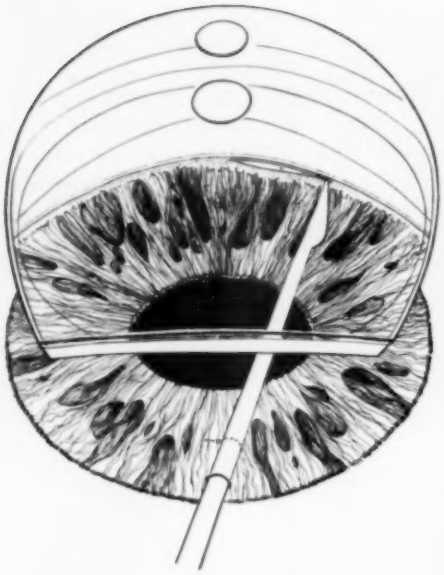

Fig. 8 (Shaffer). Drawing, illustrating goniotomy incision.

tact lens can be moved about to give optimum visibility. Then, using the puncture site as the fulcrum, a 60-degree trabeculotomy is done as indicated on the diagram (fig. 7). The knife blade is then rotated

Figures 9-20 show various stages in performing goniotomy on a cat's eye. Text on page 97.

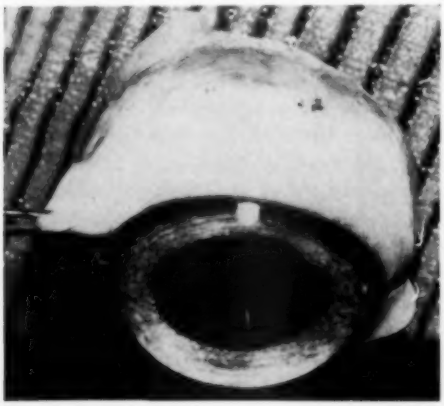

Fig. 9 (Shaffer). Positioning of cat's eye at edge of wooden block.

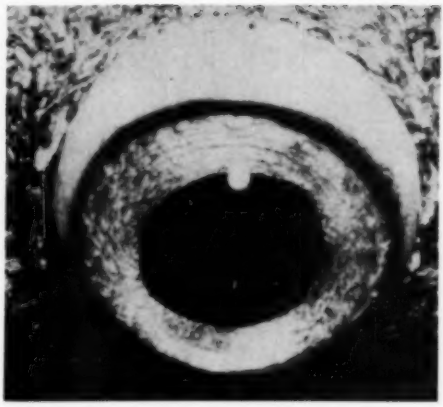

Fig. 10 (Schaffer). Fixation of eye.

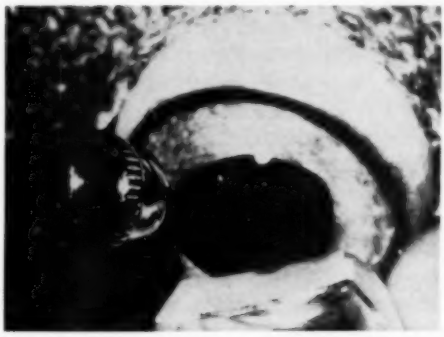

Fig. 11 (Shaffer). Instillation of saline under contact lens.

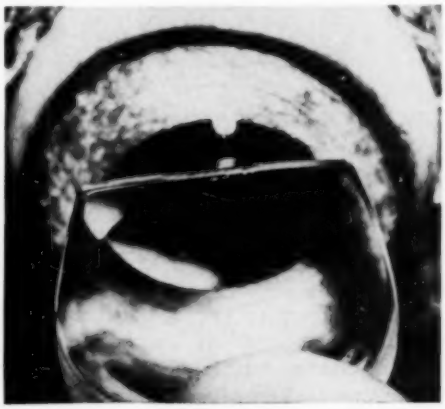

Fig. 12 (Shaffer). Lens in position

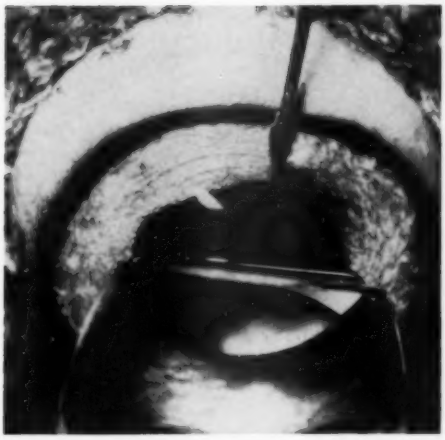

Fig. 13 (Shaffer). Position of puncture.

180 degrees as indicated and the incision carried 60 degrees in the other direction. If the incision were started at one end and carried for 120 degrees, the blade would be disengaged from the arc of the trabeculum in the central incision because the diameter is greater centrally than at either end. If the knife is twisted farther than 60 degrees, aqueous is apt to leak from the puncture site, and it is also difficult to maintain accurate visual control of the knife tip. An incision which goes back into the anterior ciliary body will produce severe and possibly disastrous bleeding. One which goes

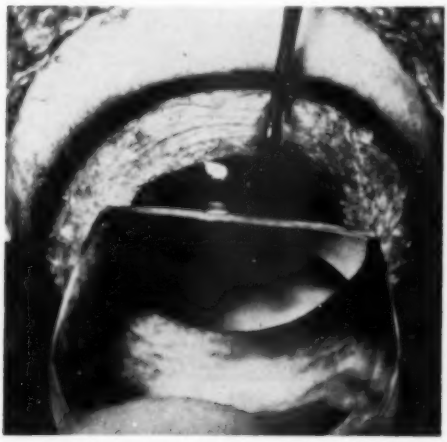

Fig. 14 (Shaffer). Knife in anterior chamber.

Fig. 15 (Shaffer). Bubble formation resulting from lens being held too close to site of puncture.

anterior to Schwalbe's line is therapeutically useless. One which goes into the sclera tends to fail because of fibrous proliferation. This is the reason visual control is so essential.

As can be seen by the diagrams, two thirds of the circumference may be goniotomized from the temporal side in two procedures. If the pressure is still not normalized, the technically more difficult temporal goni-

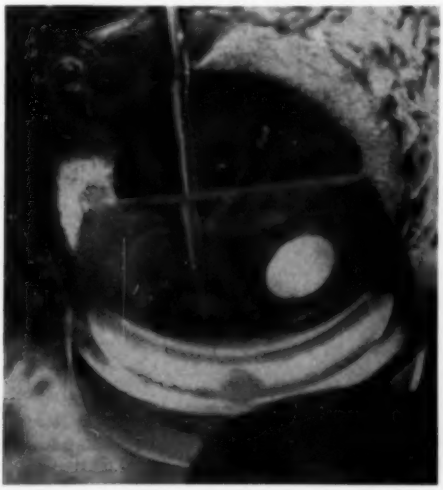

Fig. 16 (Shaffer). Removal of bubble by rotating lens away from puncture site.

Fig. 17 (Shaffer). Goniotomy incision in cat's eye.

otomy, with the knife passed over the bridge of the nose, can be done as the third operation.

7. Removal of knife

The knife should be removed smoothly and quickly keeping its handle parallel to the iris to avoid the lens. The back of the blade should be pressed toward the corneal incision to avoid enlarging it.

8. Turning of patient's head

The patient's head should now be quickly turned 180 degrees toward the surgeon. This places the goniotomy incision up and the puncture site down. A slow flow of

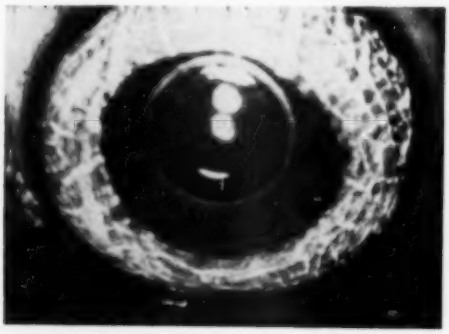

Fig. 18 (Shaffer). After goniotomy, eye is rotated 180 degrees, puncture site below. Air injected.

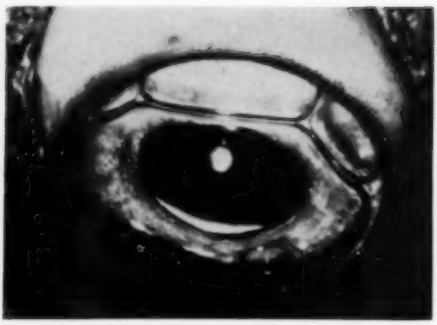

Fig. 19 (Shaffer). Air filling anterior chamber.

venous blood should now run down from the goniotomy incision and out the puncture wound.

9. Insufflation of air

It would be ideal to fill the anterior chamber with saline but in my experience it is much easier to hold air in the chamber than saline. I have never seen air blockade, probably because these eyes have such deep anterior chambers. Air blockade of the pupil is a possibility, however, and I attempt to restore two thirds of the chamber with air and the rest with saline. The air is injected with a Goldstein anterior chamber irrigator with a curved flattened silver-tipped needle which depresses the back of the puncture incision as the air is injected. If it is not

Fig. 20 (Shaffer). Use of Zeiss operating microscope in practice goniotomy.

well retained the flat back side of the irrigating tip or a muscle hook held over the slanting puncture incision for a minute is usually sufficient. Aureomycin ointment is instilled and an aluminum shield is taped over the eye.

D. Postsurgical technique

1. Position of head

For 12 to 24 hours, the patient's head is kept turned toward the side of the puncture wound. This keeps the goniotomy incision upward so that blood can run away from it and the air rising into the angle can keep the iris away from the raw edges to avoid anterior synechias. Usually this position can be accomplished by a wristlet fastened to the bed, holding the baby's body toward that side. Within three days blood has largely disappeared from the anterior chamber.

2. Medication

Neosporin ointment is instilled daily. Pilocarpine (two percent) is started three times a day after 48 hours. The child is dismissed in three days if the eye looks satisfactory.

3. Re-examination

The child is re-examined one month after the goniotomy, with all equipment prepared to proceed with another goniotomy if tension is elevated. If tension is normal, pilocarpine is continued but stopped five days before the next examination under anesthesia two months later. If tension is still normal, the child is rechecked at three-month intervals for one year, twice in the next year, and yearly thereafter.

Practice goniotomy (figs. 9 through 20)

The two essentials in performing skillful and safe goniotomies are thorough knowledge of the gonioscopic appearance of the infant angle and adequate practice in the technique of goniotomy under gonioscopic control. A good gonioscopist can quickly acquire a knowledge of the infant angle by gonioscoping babies who are under anesthesia for some other purpose. The surgical skill can be obtained by practicing on animal eyes, fastened by toweling and thumbtacks to a wooden block. The various stages in performing goniotomy on a cat's eye are beautifully shown in the pictures taken by Miss Diane Beeston of the Glaucoma Clinic of the University of California.

Summary

This paper presents in outline form the salient features of the operating-room examination, technique of goniotomy using either a loupe or the Zeiss operating microscope, and the postsurgical care of the patient with congenital glaucoma. By a photographic outline, a method is presented of practicing goniotomy on animal eyes.

University of California
Medical Center (22).

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the time of drainage the point selected is

DRAINAGE OF SUBRETINAL FLUID IN RETINAL DETACHMENT SURGERY*

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INTRODUCTION

The two most critical points in retinal detachment surgery are: (1) The localization of the retinal breaks and (2) the drainage of the subretinal fluid. Failure to accomplish either of these two objectives adequately is responsible for most failures to reattach the retina. In this paper an analysis will be made of the indications, contraindications, and techniques of accomplishing the drainage of the subretinal fluid. The reason for draining the subretinal fluid is to cause the retina to approximate the choroid as closely as possible, especially over the areas of diathermized choroid under and around the retinal breaks.†

LOCATION AND TIME OF DRAINAGE

There are several factors to be considered in deciding at which point on the globe to attempt drainage of the subretinal fluid. One of these factors in selecting the drainage point is its relationship to the retinal breaks. If the breaks are small their location need not influence the drainage site. However, if the breaks are large, with direct exposure through a large area to the vitreous, it is theoretically wiser to drain away from the site of the breaks. This is done so that a direct path will not be available for free access of vitreous through the large break directly out of the eye through an overlying perforation site.

In general, it is usually safer and easier to drain at the point where ophthalmoscopy has indicated most of the subretinal fluid to be.

Since complications such as retinal perforation or vitreous prolapse can occur through the drainage site, it is felt desirable to have this site surrounded by diathermy. Therefore, in the case of a retinopexy (simple diathermy)it is best to obtain the drainage within the diathermy barrage or between the diathermy barrage and the ora serrata (fig. 1). Similarly, if a scleral buckle is being performed it is usually preferable to obtain the drainage in the bed of the buckle where the diathermy has been applied (fig. 2). Also, the infolding of the buckle at the drainage point gives additional security in case of these complications.

It may be noted that there is one disadvantage to draining in the bed of the buckle. After the drainage point stops leaking subretinal fluid it is wise to pull up the sutures bridging the buckle, tying only one loop of each suture, and then to examine the fundus. If ophthalmoscopy indicates the buckle is in contact with the retinal break areas and also that the buckle can be closed, the sutures may be tied. If, however, there is considerable subretinal fluid remaining which prevents approximation of the retina to the

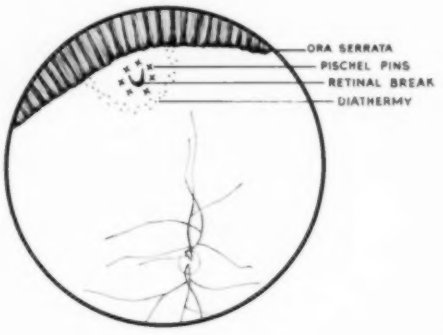

Fig. 1 (Schwartz). Seven Pischel pins inserted to surround the location of the retinal break.

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† If the retina is very close to the choroid in the area of the breaks, it may not be necessary to drain the subretinal fluid at all.

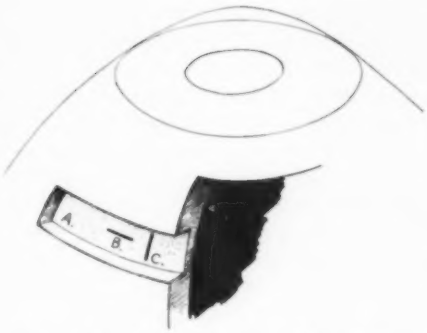

Fig. 2 (Schwartz). Sclerotomy in bed of lamellar resection. (A) Bed of resection after lamellar strip of sclera has been removed. (B) Sclerotomy parallel to length of resection (and also parallel to corneoscleral limbus). (C) Sclerotomy radial to corneoscleral limbus and therefore less likely to perforate an emissary vortex vein or a long posterior ciliary vessel.

buckle or prevents closure of the buckle, it is necessary to secure further drainage. The sutures must then be loosened to obtain further expression of subretinal fluid. This is sometimes technically difficult besides which repeated tightening and loosening of the sutures tend to weaken them as well as the sclera in which they are placed. For this reason some surgeons prefer to drain outside the buckle area and then surround the drainage point with diathermy.

Another factor sometimes considered is that of the relative dependency of the drainage point. It is often suggested that if drainage is done inferiorly, for example, at the 6-o'clock position on the globe, it is apt to be more effective than when done superiorly since gravity would aid in drainage. Practically, this is not relevant because at the time of drainage the point selected is seldom dependent, but rather is rotated forward so that there is easy access to it surgically. Thus, even if drainage is attempted at the 6-o'clock position the eye is generally rolled upward so that this position is least dependent at the time of puncture. Since practically all drainage takes place at the time of surgery rather than subsequently it seems that this factor is not important or valid.

The opportune time for drainage during the course of the operation is after placement of the diathermy in the case of retinopexy, or after placement of the diathermy and the passing of the sutures in the case of a scleral buckle. The reason for this is that if drainage is obtained first, diathermy is placed through a wet field which makes it less effectual and more apt to spread diffusely over the surface of the sclera without penetrating to the choroid. In addition, should complications ensue during drainage, it is more difficult to carry out additional procedures such as placing the sutures of a scleral buckle.

Techniques of drainage

Four techniques for obtaining drainage will be considered: (1) Multiple pins; (2) sclerotomy or "cut down"; (3) multiple perforations with the electrode; (4) punctum dilator (fig. 3).

1. Multiple pins

The rationale of the multiple pin method for obtaining drainage of subretinal fluid is: (a) To provide multiple places for drain-

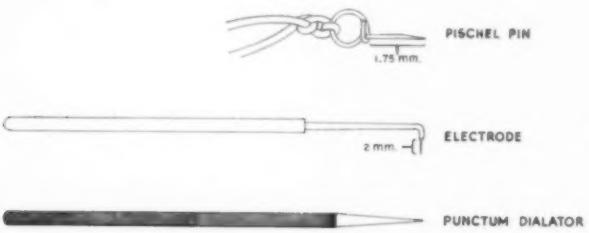

Fig. 3 (Schwartz). Instruments used to obtain drainage of subretinal fluid.

age so that if one opening is inadequate, one or more of the others may suffice. (b) To allow slow emptying of the subretinal fluid and gradual settling of the retina in order that it is not dragged to one eccentric point, resulting in traction folds due to the abnormal insertion of the retina on the choroidal envelope.

The technique of multiple pins may be used quite safely if it is applied in cases where the retina is elevated six or more diopters. However, it is frequently employed where the retina is elevated less than this amount, and the incidence of retinal perforation is correspondingly increased. Should the retina be elevated less than three diopters the use of multiple pins makes perforation commonplace, and they should not be used under these circumstances.

The important points in this technique are:

a. *The multiple pins* are usually placed to surround the break (fig. 1). However, if the retina is extremely flat in this area, and there is considerable subretinal fluid elsewhere, their location can be varied to coincide with the position of the greater volume of subretinal fluid; this would be safer with less danger of perforating the retina. It has been shown[1,2] that the adhesion of the retina to the choroid is stronger in the region of the perforations, inasmuch as the episclera can grow through here easily and form a firm scar between the two layers. This is an additional reason for placing these perforations around the breaks, since this is where dense scars are most desirable.

b. *The pins should be inserted* perpendicular to the surface of the sclera with a short quick stab. They must not be pressed in slowly, thus indenting the sclera, since this brings the pins closer to the retina and makes its perforation more likely (fig. 4).

c. *The pins are applied* using the diathermy current so that they penetrate more easily. This current should be applied for only a very short time, minimizing the danger of burning a hole in the underlying retina.

d. *The pins should be long enough* to per-

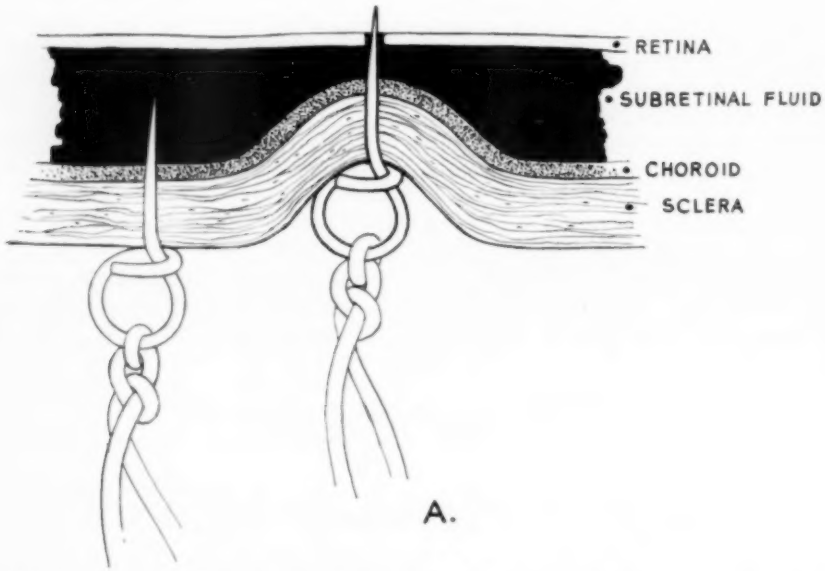

Fig. 4 (Schwartz). (A) Slow, forceful scleral indentation with pin, bringing its tip close enough to perforate the separated retina.

forate the choroid, but should not touch the retina. Their length is therefore not absolute, but varies with the scleral thickness in different eyes as well as in different parts of the same eye. It is especially variable and unpredictable in an eye that has been previously operated upon.

e. *Insertion of these pins* also has localizing value if the diathermy mark used for localization does not appear on the retina. If the retina is elevated more than three or four diopters, the marks are less apt to show on the retina following surface or partial penetrating diathermy applications. After the pins have been placed, ophthalmoscopy may show their location around the break, since frequently they will be visible even when the retina is detached more than this amount. The previous localization is thereby confirmed.*

f. *Withdrawing of the pins* should be done quickly and preferably all at the same time. Suture material attached to the pins aids in simultaneous withdrawal. Should fluid leak out through some of the openings while some pins are still in place, the retina may settle on those remaining pins and be perforated by them (fig. 5).

It has been postulated that drainage of the subretinal fluid continues through the perforation openings after the operation has been terminated, but this has not been proven. It seems unlikely that it occurs to any significant degree.

The dangers and difficulties of this technique are as follows:

a. *Perforation of the emissaria,* resulting in severe intraocular hemorrhage. This may

* This feature is less important when the highly accurate method of scleral depression under ophthalmoscopic control is used for localization of the breaks.

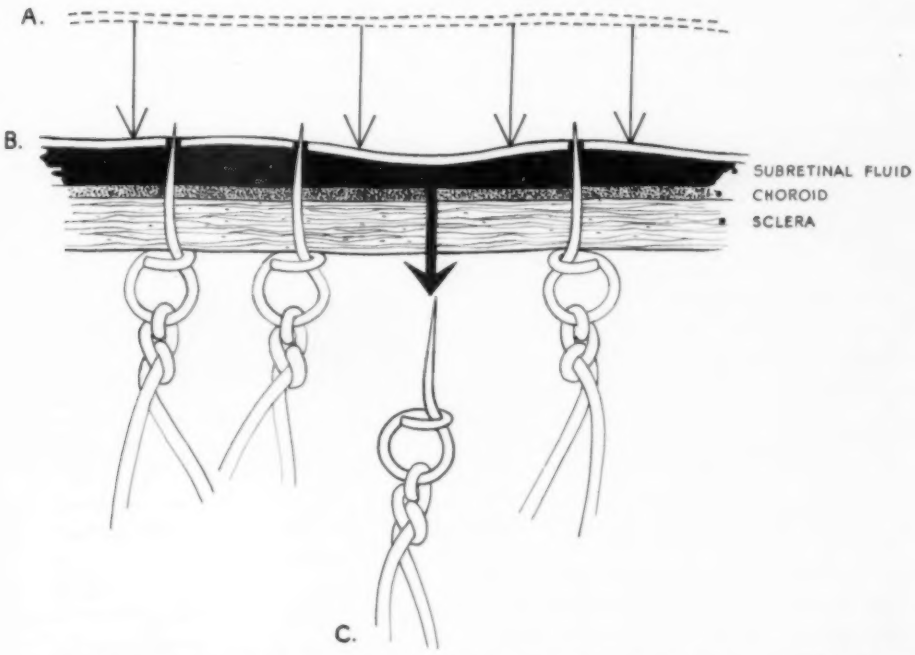

Fig. 5 (Schwartz). (A) Original position of detached retina. (B) Retina settling onto remaining pins. (C) Pin accidentally withdrawn, allowing leakage of subretinal fluid through this opening. The retina is thus allowed to settle onto the remaining pins, with resultant multiple retinal perforations.

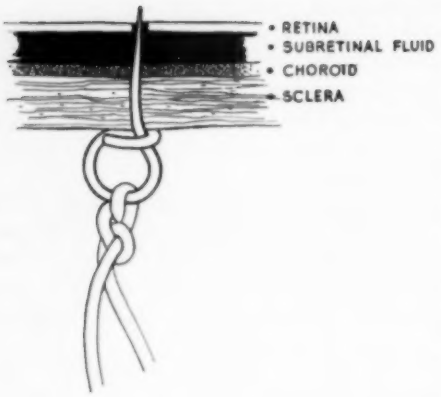

Fig. 6 (Schwartz). Pin perforating retina in eye with shallow retinal detachment. The retina is too close to the choroid to allow safe use of pin.

be due to damage to the long posterior ciliary vessels which can be avoided by not perforating in the horizontal meridians. The pathways of these vessels can usually be observed as lines through the sclera. Perforation of the vortex vein emissaria can be prevented by an acute awareness of their existence and by consciously searching them out and identifying them when working behind the equator. Their position is variable so that one must be constantly alert to identify them before perforating. Preferably the perforations should be made at least two millimeters away from the pathway of the emissaria in their trans-scleral course.

b. *Perforation of the retina.* Direct perforation due to a pin can occur if its length is longer than the combined thickness of the sclera, choroid, and subretinal fluid layer at the point of perforation (fig. 6). Allowing an average thickness of one millimeter for the sclera and choroid combined, a 1.75-mm. pin would be theoretically safe if the retina were at least two and a half diopters elevated.* Two factors, however, make this estimate inexact. The first is that the sclera and choroid vary greatly in thickness, and an average cannot, therefore, be postulated. The sclera may vary in thickness from between one or two-tenths of a mm. up to as much as two mm. in some re-operated eyes. A second is that when the sclera is indented with a pin, and even though three to four diopters of separation between the choroid and the retina may be originally present, the indentation may so narrow this distance as to allow the pin to pierce the retina (fig. 4).

c. *The temperature of the pin* may be such that even should its point be separated from the retina by a distance of one or two diopters it may still burn a hole in it (fig. 7). For this reason, it is emphasized that the current should be turned on long enough to allow the pin to pierce the sclera and choroid, but no longer.

d. *One pin may come out prematurely,* allowing leakage of subretinal fluid and permitting the retina to settle onto the remaining pins. This results in one or more perforations of the retina by these pins. Should a pin fall out, the situation may be handled in one of two different ways:

1. The pin may be immediately replaced if sufficient subretinal fluid is present so that

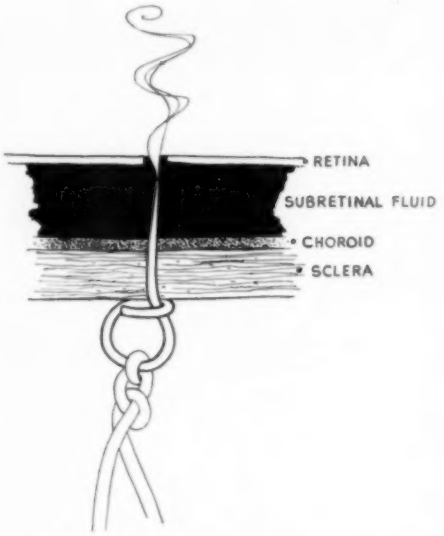

Fig. 7 (Schwartz). Hole burned in retina by heat of pin tip, even though pin has not touched the retina.

* One millimeter equals approximately three diopters in the average eye.

there is no danger of perforating the retina by reinserting it. This is somewhat hazardous, however, since the retina may have settled considerably at this point due to leakage of subretinal fluid through the resultant opening.

2. All the remaining pins may be quickly withdrawn to prevent the retina from settling onto them. This is probably the safest course. It may, however, complicate the remainder of the operation, especially if a contemplated scleral resection has not been completed.

e. *Occasionally, after withdrawal of the pins,* a negligible amount of subretinal fluid drains from the eye. The causes of this are several:

1. The pin may be too short to penetrate the thick sclera and choroid. This factor frequently can be evaluated by ophthalmoscopy subsequent to insertion of the pins. Should they be visible in the subretinal space, it is obvious that they are long enough to go through the choroid and sclera. If the retina or ocular media are too opaque to allow accurate visualization of the subretinal space, ophthalmoscopy cannot be relied upon. Though this space is occasionally obscured to direct ophthalmoscopy, it is rarely hidden from penetration by the Schepens binocular ophthalmoscope employed by one competent in its use. If the pins are too short, and if it is certain that there is sufficient separation between the retina and choroid to allow the use of a longer one, the latter may be inserted instead. In a primary operation the 1.75-mm. pins are usually adequate. In fact, they may be excessive in length and may cause perforation of the retina. However, in a secondary operation, the sclera may be considerably thickened so that occasionally the longer pin may not penetrate the subretinal space.

2. A second reason for failure to obtain fluid drainage is that the pin may have been placed in an area where there is insufficient subretinal fluid. This can be avoided by careful ophthalmoscopic evaluation prior to its insertion. It is not sufficient to rely upon ophthalmoscopic examination performed before surgery, since during the operation the fluid may shift and cause a different distribution due to manipulation.

3. A third reason for failure of fluid drainage may be that the fluid in the subretinal space is too thick and viscid to seep through the small perforation made by the pins. Suction with a medicine dropper over the site of perforation may overcome this difficulty. Sometimes, considerable subretinal fluid may be withdrawn in this manner. Enlarging the opening with a punctum dilator may be of value. This technique is occasionally successful, but it is a somewhat uncontrolled procedure inasmuch as it is difficult to accomplish under ophthalmoscopic visualization, and the punctum dilator may therefore perforate the retina if pushed too far.

The question may be asked as to why retinal perforations are harmful if diathermy is directly under them to seal off these surgically produced retinal breaks. There are three main reasons why a retinal perforation under these circumstances is definitely disadvantageous:

1. It causes a disturbance of the vitreous with resultant vitreous strands, retinal traction, and potential retinal folds.

2. Retinal hemorrhages are more common after such perforation.

3. If the retina is not reattached by the surgery (and this failure occurs in approximately one third of all primary operations), new retinal breaks have been created which have to be subsequently sealed if the detachment is to be successfully repaired. Sometimes these newly created breaks are extremely difficult to find, and the chances of failure, therefore, are increased at the second operation.

2. Sclerotomy

With this technique, an opening is made directly through the choroid without scleral intervention so that there is little problem of a small opening in the latter being clogged by coagulum and thereby obstructing drain-

age. If this technique is used properly, an electrode needle is very unlikely to perforate the retina, even with flat retinal detachments. In addition, the choroid can be perforated without using electric current, thus eliminating heat within the eye and close to the vitreous.

This technique of drainage is best used where a lamellar scleral resection has been performed and the cut-down is in the bed of the lamellar resection. Under these circumstances there are a very small number of scleral fibers remaining, and it is relatively simple to prolapse the choroidal knuckle over the level of the markedly thinned scleral lips of the sclerotomy opening.

If complications, such as retinal or vitreous prolapse occur, the consequences are less serious by virtue of their occurrence over the area of the buckle which is indented and makes the resulting vitreous traction less harmful. If done carefully, this technique is quite safe even if there is minimal retinal separation at the point of the sclerotomy. Of course, some subretinal fluid must be present at this point to secure drainage, but the danger of perforating the retina in the presence of a somewhat shallow detachment is less than that following any of the other techniques.

The procedure may also be used when doing a retinopexy but here it is a little more difficult to prolapse the choroid up to the level of the somewhat thicker scleral lips.

The technique which seems best is that developed by Schepens and his associates on the Retina Service at The Massachusetts Eye and Ear Infirmary. The sclerotomy is two to three mm. in length and may be either radial or parallel to the limbus. Each direction has its own merit. If radial (fig. 2-C) there is less danger of severing an emissary vessel. Should the sclerotomy be performed in the bed of a lamellar scleral resection, an incision parallel to the long axis of the resection (fig. 2-B) (and therefore usually parallel to the limbus) probably is closed better after the buckle is sutured.

When the cut-down is through or almost through all of the scleral fibers, the margins of the sclerotomy wound may be coagulated with diathermy so as to cause the scleral fibers to retract slightly from the opening and thus provide easier access to the choroid. An iris spatula may be passed under the scleral lips to ensure that it has been completely perforated, as well as to free the thin lamellar connections between the sclera and choroid.

By slight pressure to one side of the opening (fig. 8, arrows), a small choroidal bulge can be made to appear between the lips of the sclerotomy and to present sufficiently so that it is slightly higher than the scleral level. This prolapsed knuckle of choroid is then perforated with a fine, sharp electrode which is held tangential to the scleral surface so that the needle does not pass within the scleral level and therefore does not threaten the retinal and vitreous integrity (fig. 8-A).

If one proceeds in this manner, drainage is almost always obtained. Such drainage may be supplemented by pressure upon the sclera with an applicator stick, rolling it toward the sclerotomy opening. If the sclerotomy is held open by slight pressure just to one side of it better drainage is permitted. When no more fluid appears, the fundus should be inspected to see if more is present, rather than exerting forceful pressure upon the globe which may cause retinal and vitreous prolapse and consequent disaster.

The dangers and difficulties of this method are:

a. *Perforation of the long posterior ciliary vessels or vortex vein emissaria.* The same precautions should be used as discussed under the use of multiple pins.

b. *The incision may be too deep,* resulting in perforation of the choroid with the knife. This is not common in a primary operation because, having cut through the last few scleral fibers, the knife usually pushes away the choroid without cutting into it. Occasionally, however, a sharp knife will incise the cho-

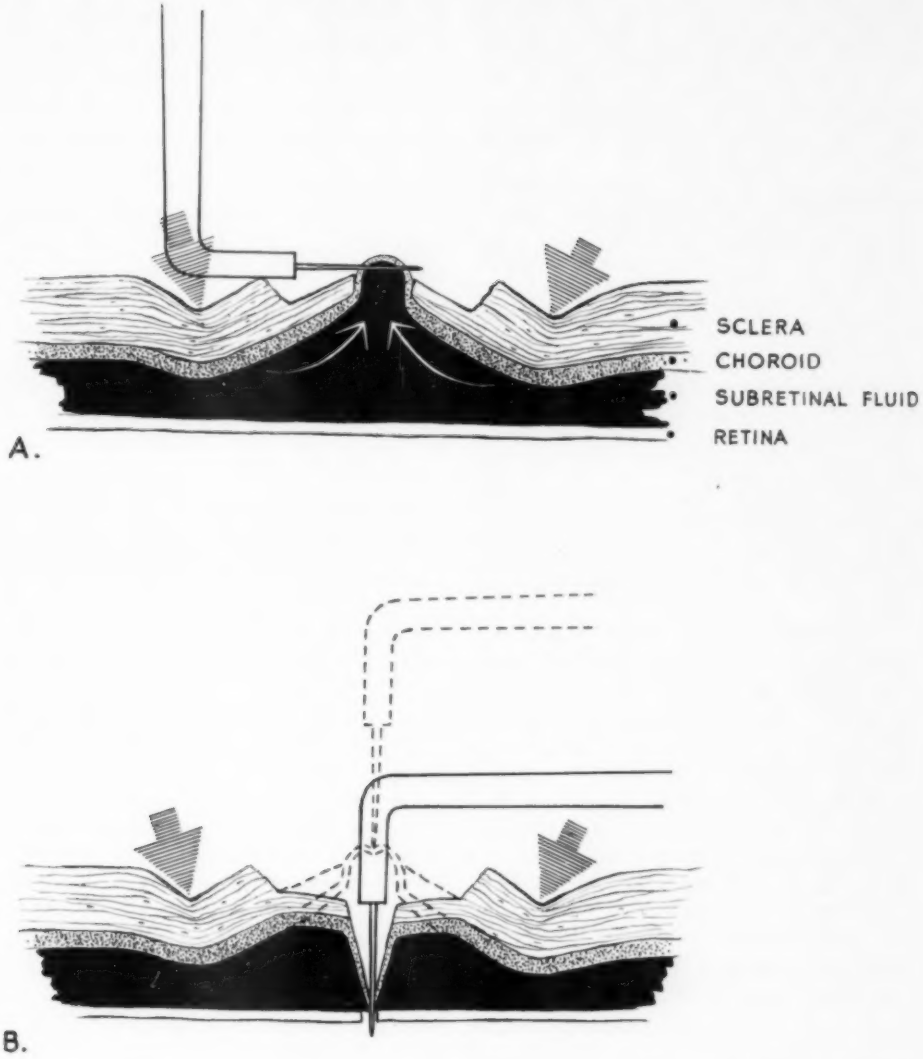

Fig. 8 (Schwartz). (A) Electrode needle applied correctly tangential to scleral surface to perforate the choroid safely for drainage of subretinal fluid. (B) Electrode incorrectly applied, pushing choroid ahead and making retinal perforation more likely. Arrows indicate slight scleral pressure to encourage prolapse of small choroidal knuckle through sclerotomy opening.

roid and result in drainage of subretinal fluid. This is more common in re-operations wherein the choroid may be scarred and adherent to the sclera. As a rule, this is not harmful, but a choroidal vessel may be severed as a consequence, resulting in considerable hemorrhage. If this hemorrhage drains out of the eye it is not too serious, but if the bleeding is heavy into the eye the effects can be disastrous. Should the cho-

roidal laceration be extensive, retinal and vitreous prolapse may occur through it; these are serious complications.

c. *It may be difficult to prolapse a choroidal knuckle through the sclerotomy opening.* This is usually due to a few remaining scleral fibers because the sclerotomy is not completed. All of the scleral fibers should be cut, and this can be evaluated by passing a spatula between the choroid and sclera at the margin of the wound.

d. *There may be difficulty in puncturing the choroidal knuckle with the electrode.* To obviate this, it is important that a sharp electrode is available, and also that perforation is tangential to the scleral surface (fig. 8-A). If the electrode is applied perpendicular to the surface of the globe (fig. 8-B) the choroid may simply be pushed into the eye without perforating it. With more pressure, the electrode may suddenly perforate the choroid as well as the retina in an uncontrolled fashion.

e. *A small amount of subretinal fluid may drain forth and drainage suddenly cease.* Ophthalmoscopy should be performed at this point. If a buckle has been prepared, the sutures bridging it should be tightened as much as possible just prior to ophthalmoscopy. Ophthalmoscopy may show that there is no more subretinal fluid. It may also show that subretinal fluid is still present, but the retina may appear to have been pushed down into the choroidal wound, thus plugging that drainage point. It may also be that the choroidal opening is simply plugged with coagulum or thick subretinal fluid which prevents further egress. If ophthalmoscopy reveals residual subretinal fluid, the sutures of the buckle may be loosened and the sclera massaged gently with a cotton tipped applicator over the areas of the trapped fluid, massaging toward the perforation site. Occasionally this will unplug the opening and allow further drainage. If this is unsuccessful, a second site where subretinal fluid is definitely present should be selected for additional sclerotomy and drainage.

f. *A small hemorrhage occurs at the point of perforation of the choroidal knuckle, but no subretinal fluid comes forth.* Under these circumstances it is probably wise to select a different site for sclerotomy and drainage. Allowing the small hemorrhage to bleed outside the eye will usually eliminate serious consequences.

The principal disadvantage of this technique of drainage is that it requires meticulous attention to detail. If not done carefully, serious complications such as retinal and vitreous prolapse may occur. However, in experienced hands, it is an extremely effective way of draining subretinal fluid and will frequently accomplish this purpose in cases where the use of multiple pins will not, or cannot do so safely.

3. Electrode perforations

The 1.5- or 2.0-mm. electrode is plunged through the sclera at several places in quick succession. Due to the smaller diameter of the electrode needle (0.2 mm.) this usually does not work so well as multiple pins (with a base of 0.3 mm.) if the "coagulating current" is used. However, should the higher frequency "cutting current" be used, the smaller openings seem to stay patent enough for adequate drainage of the subretinal fluid. This technique is somewhat uncontrolled insofar as one cannot evaluate ophthalmoscopically the depth of electrode perforation and whether or not the retina is being perforated. In addition, if the first perforations allow some subretinal fluid to escape, subsequent ones are attended by an increasing hazard of retinal damage as it settles down closer to the choroid.

4. Punctum dilator

A sharp punctum dilator may be rotated back and forth between the fingers so as to cause it to perforate the sclera and choroid and allow the drainage of subretinal fluid. It is difficult to control the depth of the perforation by ophthalmoscopic observation while inserting the dilator. Unless it can be

observed accurately by ophthalmoscopy at the time of perforation, the technique is also somewhat uncontrolled and perforation of the retina may inadvertently occur.

Intravitreal injection

An adjunct to drainage by any of the methods discussed is the intravitreal injection of air, saline, or vitreous. This causes an increase in the intraocular pressure and helps eliminate the subretinal fluid. Caution must be exercised with this procedure if a sclerotomy has been used for drainage because of the danger of retinal and vitreous prolapse through this relatively large opening. With the use of multiple pins this hazard is less. A second disadvantage of intravitreal injection is the violation of the vitreous cavity which may result in the formation of vitreous strands and subsequent traction originating at the site of the injection.

Discussion

Drainage of subretinal fluid in retinal detachment surgery has been effectively accomplished by varying techniques. During the process of draining subretinal fluid it is desirable to avoid certain complications. Among these are: (1) Retinal perforation; (2) retinal distortion, or uneven distribution of the retina against the wall of the globe; (3) vitreous disturbance; (4) intraocular hemorrhage; (5) prolapse of the retina or vitreous.

No one method has proved ideal. An awareness of the drawbacks and difficulties of any given method should allow intelligent application and selection in relation to the individual eye and to the type of surgery performed.

Summary

Drainage of subretinal fluid is a critical part of retinal detachment surgery. The purpose, site, and timing of the drainage have been discussed. The four main methods of obtaining drainage have been described. The difficulties and complications of these methods have been brought out. No single method has been found to be ideal and to answer all needs safely. Knowledge of the advantages and disadvantages of each allows intelligent application in any given patient.

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MIMOSINE CATARACT*

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In 1944 Yoshida[1] reported the development of cataract in young rats fed a diet containing seeds or leaves of Leucaena glauca Benth, or the toxic substance extracted from this leguminous plant. Previously, other ill effects such as loss of hair and stunted growth had been attributed by various workers to the ingestion of such feed.[2-5] The eye changes have not received attention since the initial observation of Yoshida. The present paper provides infor-

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mation on this drug-induced lens opacification and other ocular lesions which have been investigated with clinical, histologic, and cytologic techniques. In addition, data on the effect of local drug administration were collected and a brief study was carried out on the influence of B vitamins on the development of the ocular damage. A short description of some of the results has been given in the symposium on the "Etiology of cataract" at the XVIII International Congress of Ophthalmology held in Brussels in 1958.

Mascré[6] first extracted a definite toxic principle from the leaves and seeds of Leucaena glauca which he called leucenol. Later this substance was shown to be identical with mimosine isolated from Mimosa pudica.[7] Synthesis of the compound was achieved in 1949 by Adams and Johnson[8] and its structure was proven to be β[3-hydroxy-4-pyridone]-α-amino propionic acid as first suggested by Wibaut.[9] The material used in the present work was isolated from seeds of Leucaena glauca in crystalline form by Dr. R. K. Kielly or was prepared according to her instructions.

Technique

The experiments were carried out on young male Sprague-Dawley rats. The animals, five to six per litter, were 25 days old when feeding was started. The experimental diet consisted of powdered stock pellets to which were added 5.0 or 10 gm. per kg. of mimosine. For controls, one or two animals of each litter received the powdered stock diet. Body weight, food consumption, and gross appearance of the animals were recorded weekly. The rats were examined with the Goldmann slitlamp repeatedly during the first week, then at weekly intervals and were killed in litter groups on the third, fifth, seventh, 14th, and 21st day after the feeding was begun. The lenses of the right eyes were fixed in Carnoy's solution and submitted to the Feulgen reaction; whole mounts of the lens epithelium were prepared except in later stages of cataract development when this technique was unsuccessful. A great number of these lenses were also bisected meridionally and examined under low magnification. All left eyes were embedded in celloidin, cut in 10μ thick sections, and stained with hematoxylin-eosin. Eyes from 46 animals were studied in this way.

In addition, two litters were treated with instillations of 0.5-percent mimosine solution into the conjunctival sac of both eyes twice daily for three weeks. These animals were fed the powdered stock diet whereas a control group received a diet containing 0.5-percent mimosine. Material from two other litters was prepared for electron microscopic studies (Dr. T. Wanko and M. Gavin) and quantitative histochemical examination according to the technique of Lowry (Dr. R. Kuhlman). Finally, three litters were used for comparing the effect of high pyridoxine and niacin levels on the toxicity of the mimosine diet.

Results

A few days after the animals were placed on the experimental diet, growth stopped and no further weight gain was noticed during the three-week observation period. The fur was ruffled in many instances, but alopecia was not observed. No death occurred in any of the experimental series.

Biomicroscopic observations. Two or three days after the diet was started, pronounced inflammatory changes developed in the anterior segment of the eyes and to some extent in the ocular adnexa. Moderate discharge from the conjunctiva was associated with engorgement of limbal vessels and, frequently, with subconjunctival hemorrhages. At about the third day the corneas developed patchy or diffuse opacities accompanied by the formation of epithelial bullae of various size. Blood extravasations were often noted in the anterior chamber and were also seen in the posterior chamber through the transparent iris. Iris hyperemia, posterior synechias, and fine occlusion membranes prevented the dilatation of the pupils and illus-

trated the severity of the involvement of the anterior uvea in early stages.

The changes advanced moderately in the following two days, with vessels growing into the edematous cornea. In most instances early superficial lens changes could be distinguished despite the cloudy cornea and miotic pupil. Such observations on the anterior lens cortex were confirmed when, five to seven days after onset of the experiment, the violent response in the cornea and iris subsided.

The cataractous changes consisted of scattered subcapsular gray dots and fine striations or superficial vacuoles in the pre-equatorial zone. Corneal scarring and vascularization, as well as the residues of the inflammatory pupillary membrane and synechias interfered frequently with the biomicroscopic examination of the posterior part of the lens. An advance of the cataractous process was definite at the two-week interval and a week later the opacification comprised a great part of the anterior and posterior cortex or had resulted in the formation of total cataract. At this time the inflammation of conjunctiva, cornea, and anterior uvea had quieted almost completely.

Observations on flat mounts of epithelium after Feulgen reaction. Attempts to examine the epithelium in whole mounts after the Feulgen reaction were only partly successful and impossible in later stages because of inflammatory adhesions between the lens and the iris. In circumscribed areas of the central and pre-equatorial zone cell nuclei were closely grouped and sometimes multilayered in early phases. This crowding of nuclei was combined with variations of cell size and shape, and with signs of pyknosis or nuclear fragmentation.

Counts of dividing cells and degenerate nuclei were carried out on six experimental and eight control preparations at the three- and five-day interval. At this time the response of cell division to the experimental condition was not uniform, but low mitotic counts of various degree were common. Striking was the number of degenerate cell nuclei, which varied from 70 to 874 per preparation with an average of 328. Eyes of normal rats of this age do not show more than 15 degenerate nuclei in the entire cell population.

Observations under the stereomicroscope. Intact or decapsulated lenses which had been subjected to the Feulgen reaction were bisected meridionally and examined under the low-power of a dissection microscope. With this procedure the distribution of cell nuclei in the entire lens could be surveyed. No cellular details were seen, but, instead, a better understanding of the cytopathologic process was obtained, which otherwise would have had to be reconstructed by the examination of many sections. Preparations of rat lenses at the one-week interval showed an accumulation of nucleated elements at the anterior pole or pre-equatorially. In the germinative zone the cell nuclei were arranged often in an irregular patchy pattern interrupted by round cell-free spaces of varying diameters. Displacement of bow nuclei or forward migration of equatorial cells was minimal, if present at all.

One week later the bow nuclei were seen to fan out backward although the rest of the picture had changed very little. Animals kept three weeks on the diet differed in severity of changes according to the litter. In a group with minor biomicroscopic changes forward and backward extension of the bow nuclei was of moderate degree. In another litter with more advanced clinical signs the nuclei were accumulated in the pre-equatorial area in an irregular fashion. Often the nuclei formed a ring pattern. The bow nuclei spread out backward in the deeper portions of the cortex and gradually assumed a more superficial location toward the posterior pole. The area around this pole, however, remained free of cell nuclei as their invasion ended abruptly at some distance from this site. Lenses which were almost completely cataractous exhibited wide scattering of cell nuclei throughout the anterior and posterior

cortex. The dark purplish line indicating the bow was moved backward and the normal architecture of the bow had disappeared.

Histologic and cytologic observations. The extent of the damage of the lens varied from litter to litter but showed a remarkable uniformity among litter mates. The characteristic initial lesion (third day) involved the epithelium of the equatorial region and consisted of an increase in cell size. The length diameters of these cells exceeded those of the control group two- to four-fold without measurable change in the size of the nuclei (fig. 1). This "hydrops" of the cytoplasm in elements of the germinative zone was combined with cell proliferation and moderate swelling of the younger nucleated fibers.

At a slightly later stage (fifth day) there was an increase in number of equatorial cells which were aggregated underneath the capsule at the point where the lens bow originates (fig. 2). The accumulated cells had assumed vesicular forms and contained degenerate nuclei.

The apparent vulnerability of the cells of the germinative zone was emphasized by the sharp delineation of the injured area which later often contained islands of homogenous, darkly eosin-stained material and nuclear debris (fig. 3). Cortical fibers and bow nuclei outside the line of demarcation of the lesion were histologically normal. The surface epithelial cells could not be well evaluated in sections, but, as mentioned above, examination of flat mounts indicated widespread nuclear degeneration and depressed cell division in this cell layer. Although a small number of superficial fibers of the anterior cortex were swollen, there was no doubt that the surface epithelium, and particularly the cells at the equatorial area, were the main sites of early injury.

In the following days (seventh day) the localized change expanded in depth and width (fig. 4). At the same time, swelling of the superficial lens fibers progressed especially in the anterior cortex. In the following week the destructive process extended from the equatorial site backward, but did not reach the posterior pole of the lens as also illustrated by observations under the dissection microscope. Bow nuclei adjacent to the equatorial region underwent pyknotic changes and, in some lenses, cystic spaces filled with granular matter resembled the cavities described in galactose and alloxan cataract.

In about one-half of the animals, the cata-

Fig. 1 (von Sallmann, Grimes, and Collins). Third day of mimosine feeding. The equatorial epithelial cells show marked swelling. (Hematoxylin-eosin, phase contrast, ×1,120.)

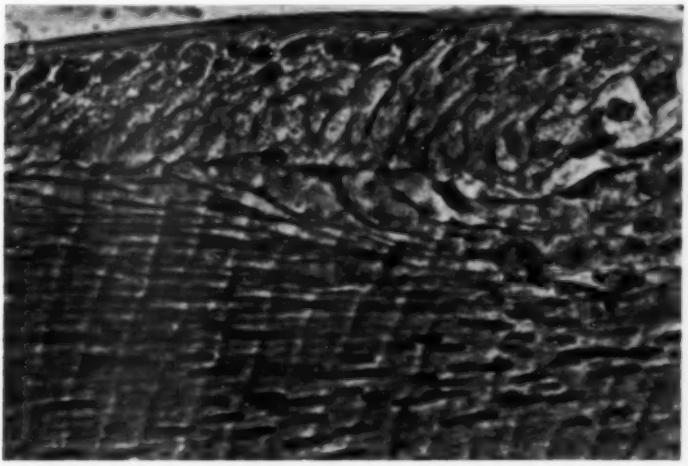

Fig. 2 (von Sallmann, Grimes, and Collins). Third day of mimosine feeding. Swollen epithelial cells and proliferated cell elements at the equator. Swelling also involves the superficial fibers whereas deeper fibers and bow nuclei are normal. (Hematoxylin-eosin, phase contrast, ×504.)

ract was complete or nearly total at the end of the third week when the experiments were terminated. Even in this late stage the pathology at the equator dominated the histologic picture. Large vesicular cells occupied adjacent areas and nucleated elements formed a broad zone which surrounded the lens nucleus posteriorly. The normal bow architecture was thus wiped out. Homogenous granular debris replaced the normal lens fiber pattern in the anterior cortex and a peculiar reticular configuration was frequently observed in a broad perinuclear zone. Superficial parts of the lens nucleus were broken up and disorganized and clefts filled with granular matter were distributed

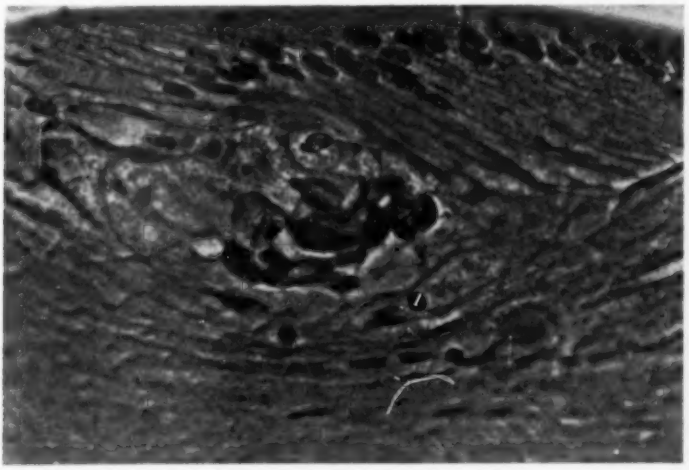

Fig. 3 (von Sallmann, Grimes, and Collins). Fifth day of mimosine feeding. Equatorial area is characterized by proliferated swollen epithelial cell and deposition of eosin-stained homogenous material. (Hematoxylin-eosin, phase contrast, ×504.)

Fig. 4 (von Sallmann, Grimes, and Collins). Seventh day of mimosine feeding. Advanced changes in equatorial area showing swollen degenerate cells and hydropic superficial fibers. (Hematoxylin-eosin, phase contrast, ×504.)

through the rest of the nucleus. Lens epithelium changes were less marked than in the earlier stages, but whole mounts could not be studied at this time.

The material submitted to electron microscopic examination* was obtained five, seven, and 14 days after the diet was started. Equatorial and central portions of the epithelium and superficial fiber layers were examined. The descriptions of pertinent changes are limited to the illustrations since detailed observation on epithelial and fiber damage in experimental cataract as seen under the electron microscope will be reported by Wanko and Gavin in the near future. The normal morphology of both the cytoplasmic constituents and the cell nuclei was disturbed. The distended cisternal configuration of the numerically increased rough surfaced endoplasmic reticulum was most striking. Mitochondria appeared swollen and showed cristae which seemed displaced to the periphery (fig. 5). The nucleoli contained clumps of electron-dense material and a core of small closely packed opaque granules (fig. 6).

Enzyme assay. In a small series Lowry's microtechnique of enzyme assay was applied to selected areas of lenses from experimental and control animals† Of the enzymes studied, determination of lactate dehydrogenase alone showed sufficient uniformity of results for tentative evaluation. The examinations were carried out in, first, epithelium and capsule, second, in parts of the equatorial area including the bow, third, at a later interval, in or at foci of cell proliferation, and fourth, at two-week intervals, at sites where the lens structure was grossly disorganized. At no time were differences observed in the lactate dehydrogenase level in epithelium and capsule between the experimental and control animals. Examination of the equatorial cortex indicated a marked, but transient, decrease of the enzyme activity on the fifth day. This decrease was not evident at the later stages. Samples from areas of proliferated epithelium exhibited about twice the activity of comparable tissue samples of control litter mates; whereas, the disorganized cortex on the 14th day revealed marked decrease of the enzyme activity.

* The electron micrographs and the interpretations were made available by Dr. Theodor Wanko.

† Microchemical studies have been carried out by Dr. Robert E. Kuhlman.

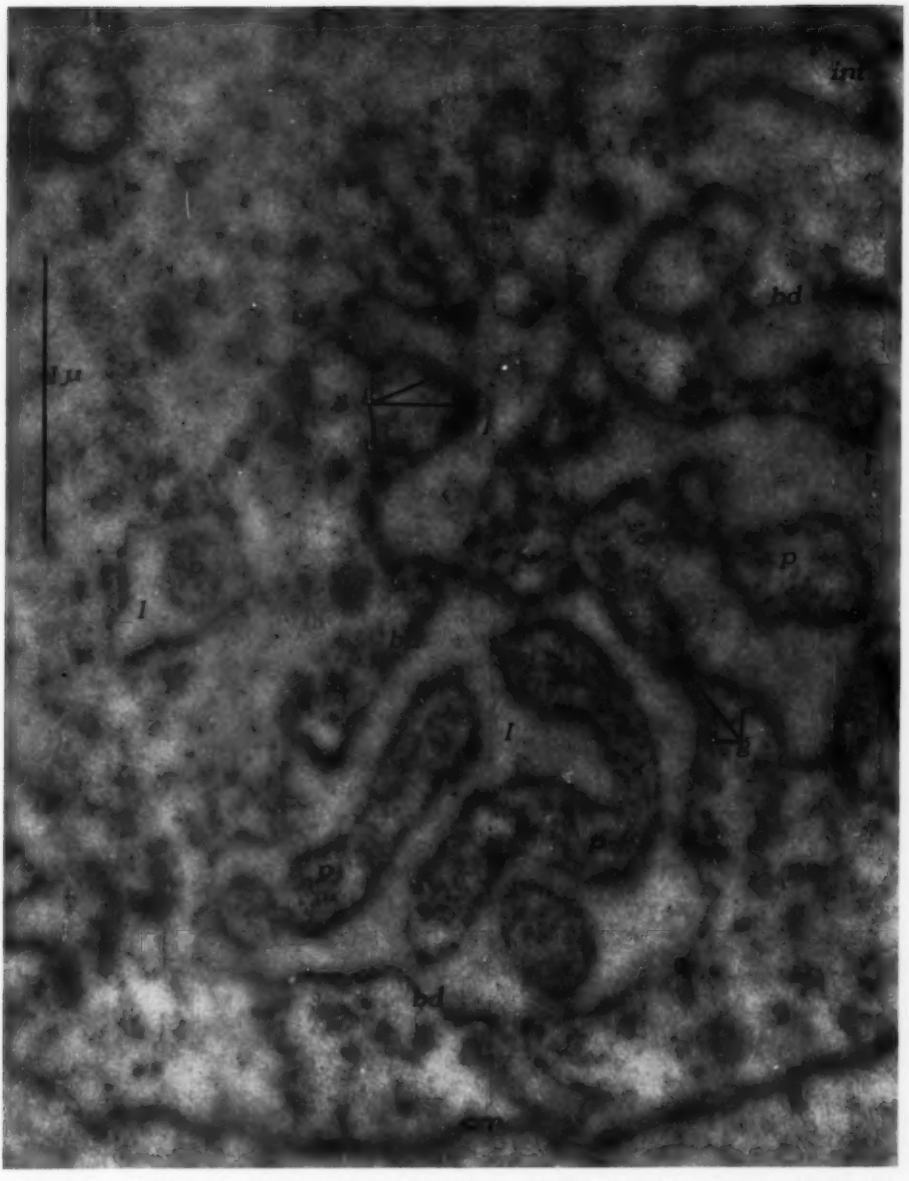

Fig. 5 (von Sallmann, Grimes, and Collins). Rat lens epithelium after five days on mimosine diet, peripheral zone. This micrograph illustrates the increase in rough surfaced endoplasmic reticulum. It assumes a cisternal configuration with a wide lumen (l) and a complicated, tortuous boundary (bd) which projects (p) in many different directions. Dense granules (g) are diffusely attached on its outer surface. A cross-sectioned mitochondrion (m) shows a homogeneous center with the cristae displaced to its periphery. Cell membranes (cm) and interdigitating cell processes (int) are designated. (Fixed with buffered one-percent osmium tetroxide at pH 7.3 for two hours. Electron micrograph approximately ×43,000.)

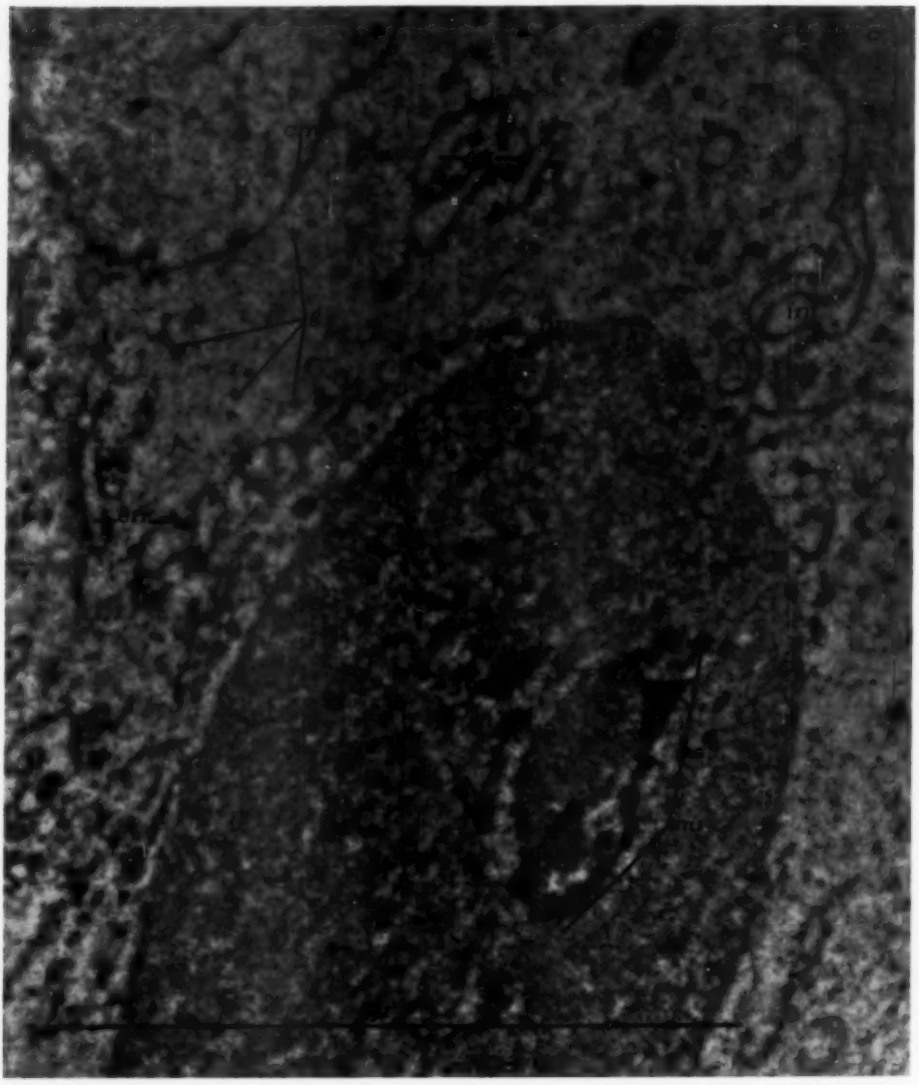

Fig. 6 (von Sallmann, Grimes, and Collins). Rat lens epithelium, after five days on mimosine diet, peripheral zone. This micrograph shows part of a lens epithelial cell with a prominent nucleus (n) in its center and a small portion of lens capsule (c) in the right upper corner. At this phase, nucleoli (nu) are found as composites which display clumps of dense material (d) scattered around a core (co) of closely packed, opaque granules. Changes observed in the cytoplasmic elements include distension of cysternal spaces between the membranes of the rough surfaced endoplasmic reticulum (err) while sparsity of internal cristae and swelling characterize the mitochondria (m). Cell membranes (cm), interdigitating cell processes (int), and nuclear membranes (nms) are indicated. (Fixed with buffered one-percent osmium tetroxide at pH 7.3 for two hours. Electron micrograph approximately ×23,600.)

Local administration of mimosine. The mimosine-induced clinical changes suggested the possibility of a local effect of the toxic substance on the eye. The compound could have been brought into the conjunctival sac during the intake of the powdered feed and produced the corneal damage, the violent vascular responses, and possibly the deeper lesions. In two litters, one-half percent solutions of mimosine were instilled twice daily in the conjunctival sac and the drop held in contact with the surface of the eye for about one minute. This procedure was repeated for 21 days. The local application failed to produce even a trace of the ocular signs characteristic for mimosine-fed rats. The control animal placed on the mimosine diet developed typical lesions as described previously. It was concluded from these observations that the toxic factor reached the eye tissue via the blood stream. Hemorrhages occasionally observed in the vitreous and frequently in the posterior chamber support this concept.

Administration of pyridoxine and niacin. The chemical structure of mimosine shows a certain similarity with that of the vitamin pyridoxine and to a lesser extent with that of niacin. Moreover, experimental cataract combined with loss of hair and inhibition of growth has been accredited to vitamin deficiencies.[10,11] An experiment has been carried out, therefore, to examine the possibility that, in this case, cataractogenesis is connected with an "antivitamin" mechanism. High levels of pyridoxine and niacin were administered in an effort to protect experimental animals against the toxic effect of mimosine.

Three litters of 23-day-old rats were used in this experimental series. One litter was placed on a diet of ground stock pellets containing 0.1-percent pyridoxine HCl and a second litter was fed a similar diet with 0.1-percent niacin added in place of pyridoxine. At this time the rats fed with vitamin B_6 received an additional 20 mg. dose by subcutaneous injection as did those rats on the niacin diet. After one day, the vitamin levels of both diets were raised to 0.5 percent and this regimen was continued for three days. During this time, the third litter received a standard stock diet. Following the period of pretreatment, all animals were started on the mimosine diet (1.0 percent) with the vitamin supplements continued at the same level.

The litter fed the mimosine diet alone and the litters which received the vitamin supplements prior to and during the consumption of mimosine did not differ from each other regarding growth. Onset and extent of the biomicroscopic signs of the toxic mimosine effect also were indistinguishable among the three experimental groups. The histologic examination of the eyes of all animals confirmed the clinical impression that the treatment with pyridoxine or niacin has not influenced the course of the mimosine-induced inflammation of the eyes or the characteristics and speed of development of the cataract. In view of the complete failure to alter the ocular and systemic mimosine effect by pyridoxine and niacin treatment, other dose levels or techniques of administration of the vitamins were not investigated.

Discussion

Feeding mimosine to young rats produces three main clinical manifestations: a syndrome of ocular lesions, stunted growth, and loss of hair of varying degree. Similar toxic signs have been observed in rabbits while horses show only alopecia. Loss of hair ascribed to the consumption of young seeds of Leucaena glauca has been reported in native women of the Dutch Indies.[5] It is not known that other organs, organ systems, or functions are affected by the ingestion of the toxic agent.

There is some similarity between the toxic effects produced by mimosine and thallium as far as cataract formation, arrested growth, and loss of hair are concerned, but neither the histopathology of thallium cataract nor the clinical course suggests that the two types of cataract are analogous.[12,13] Other exam-

ined types of experimental cataract do not bear resemblance to the ocular changes that occur regularly in mimosine-fed young rats.

The animals of the present series were observed for only three weeks. During this period ruffling of fur but no alopecia was noted. The toxic signs were limited to lack of weight gain and eye pathology.

Clinically, cornea and conjunctival vasculature were involved first. Shortly after, before lens opacities were visible, inflammatory iris changes of hemorrhagic character were noticed. Histologic examination indicated, however, that at the time of cornea and iris damage, that is, at the third day after mimosine feeding was begun, the lens epithelium had undergone degenerative changes, particularly in the germinative zone. Cataract development was thought, therefore, to be a primary effect of the toxic agent and not caused indirectly by other tissue injury.

Swelling, proliferation, and degeneration of epithelial cells at the equator preceded histologically recognizable fiber damage, and were accompanied by nuclear fragmentation of the surface epithelium as seen in flat mounts. Incipient stages of nuclear fragmentation were demonstrated electron microscopically (fig. 6). Of particular interest were changes in the ultrastructure of the cytoplasm, that is, swelling of mitochondria and distention of the rough surfaced endoplasmic reticulum resulting in a system of tubular formations of considerable diameter. These morphologic alterations may be the correlate of the increase in cell size described as the initial microscopic lesion of the germitive epithelium.

In common with most of the studied types of experimental cataract was the early depression of mitotic activity in the mimosine-treated rats, but here the degeneration of the lens epithelium followed a much more rapid course and was more extensive than usually seen. Although changes of the anterior superficial fibers developed slightly later than the injurious effects in the epithelium they may not originate from epithelial damage. More likely, the fiber cytoplasm was directly attacked by the toxic agent which diffused through the capsule and damaged epithelium. Hydrops of posterior cortical fibers were observed at a later stage and were possibly caused by the damage to the nuclei. The fanning of bow nuclei and an apparent widespread proliferation of these cell components into the anterior and posterior cortex together with fiber destruction indicated the complete disruption of tissue element organizations which led to proteolysis and full cataract.

The regression of corneal edema and of the inflammatory or vascular signs in the anterior segment of the eye after the fifth day, with the animals being continued on the mimosine diet, is unexplained. It resembles the transient nature of hair loss. With extensive damage of the lens epithelium fiber destruction must follow and the cataract is bound to become complete even if the agent had lost its toxic action as it apparently did on the other implicated tissues.

The chemical studies by enzyme assay did not permit other conclusions than a change in enzymatic activities at sites of cell proliferation and at areas of advanced tissue destruction. The significance of these results is not clear.

Summary

1. Mimosine cataract deviates in its cytopathology from any other form of experimental cataract studied so far.

2. The early cataractous changes present within three days of mimosine feeding are accompanied, but not preceded, by extensive inflammatory signs of the cornea and iris; whereas, the posterior segment of the eye, including choroid and retina, as a rule fails to exhibit signs of a toxic effect.

3. The toxic agent affects most impressively the equatorial zone of the lens epithelium, but also produces early cell degeneration in the central portion.

4. Early hydropic swelling of young sur-

face fibers anteriorly supports the concept that the toxic principle diffuses through capsule and epithelium and exerts its effects directly on the fiber cytoplasm.

5. In the later stages, disorganization of the lens histology does not permit distinction between primary and secondary fiber damage although the pathology of the equatorial area still dominates the picture until a full cataract has formed.

6. The toxic agent reaches the eye by the blood stream.

7. The failure to influence the cause of the toxic signs by feeding B vitamins suggests that mimosine does not act by an antivitamin mechanism.

Ophthalmology Branch.

ACKNOWLEDGMENTS

The authors are greatly indebted to Dr. Ruth K. Kielley, formerly R. K. Yoshida, of the Laboratory of Biology of the National Cancer Institute, for preparing the crystalline mimosine used in the greater part of this study, and to the following members of the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness: Dr. Theodor Wanko for conducting the electron microscope studies, Dr. Robert Kuhlman for the enzyme microassay, and Mr. Leo Caravaggio for the dissection experiments and counts on flat epithelial preparations.

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THE TREATMENT OF IRIS MELANOMA*

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The purpose of this report is to evaluate the manner in which 157 cases of melanoma of the iris have been handled with the idea of establishing an approach to their future management. Necessarily the criteria must be based primarily on the course the cases have taken subsequent to treatment.

The material on which this report is based consists of (1) cases seen and treated at the Institute of Ophthalmology; (2) cases seen in consultation by members of the Staff of the Institute of Ophthalmology but treated elsewhere; (3) patients operated upon elsewhere and whose tumor specimens or sections were sent to the Pathology Department of the Institute of Ophthalmology for opinion.

From the standpoint of treatment the cases fall into the following three groups: (1) those that had excisional iridectomy (63 cases); (2) those that had enucleation (72 cases); (3) those that were observed (22 cases). Patients in the third category were those who were thought to have a probable malignant melanoma based on clinical appearance and behavior but who either refused operation or were not urged to have surgery for reasons described later.

Some of the patients having an enucleation were subjected to iridectomy initially. The subsequent enucleation resulted from (1) establishment of a malignant cytology in a lesion too widespread for local excision when it had not been appreciated previously; (2) detection at the time of the iridectomy of a process too extensive to lend itself to local excision; and (3) presence of residual tumor not amenable to further local excision after iridectomy. The cases in these three groups have been listed as enucleations.

IRIDECTOMY

INDICATIONS

1. *The tumor is confined to the iris.* This implies it does not invade the ciliary body, does not extend into the filtration angle, does not infiltrate the cornea, does not show diffuse involvement of the iris stroma, and does not show evidence of extraocular extension through the anterior emissary channels.

For some unknown reason there may be a localized diffuse melanosis of the conjunctiva at or near the limbus corresponding to the sector of the iris involved. Except for the pigmentation the conjunctiva appears normal. This does not represent tumor extension but seems to be an acquisition of melanin by the potentially pigment-producing basal cells of the conjunctiva, possibly due to a melanogenic agent emanating from the iris tumor.

It may not be possible to determine from the clinical examination, including gonioscopy, whether the tumor involves the ciliary body. As will be mentioned later, it may be possible in such cases to evaluate the situation more accurately by direct inspection at the time of surgery.

2. *Established growth or signs of active change.* This must be evaluated either by very accurate measurements and drawings or by photography. In dealing with such relatively minute details, clinical impressions on the part of the patient and the ophthalmologist may be quite unreliable.

It is true that an iris lesion may show an

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accentuation of its pigment, perhaps at puberty or during pregnancy, but this does not necessarily imply active growth.

In establishing activity of a lesion the appearance of nutrient vessels in the tumor, or coursing in the iris stroma to the tumor, is significant. When the melanoma is in the periphery of the iris and it is difficult to decide if the ciliary body is involved, the presence of episcleral vessels corresponding to the location of the iris tumor is suggestive evidence of ciliary body participation.

Incomplete dilatation or "splinting" in the area of the tumor is a very pertinent observation and signifies stromal invasion. Additionally, the pupil is often distorted, being elongated toward the lesion. This appearance may be accentuated by ectropion uvea.

3. *Absence of tumor seedings.* Tumor seeds or satellites may be seen as implantations over the iris surface or in the dependent angle of the anterior chamber. It may be difficult to distinguish between a tumor seed and an iris freckle since the presence of a melanoma not only serves to accentuate the pigment of pre-existing freckles but promotes the appearance of additional pigmented patches of benign potential. If the fellow iris has comparable freckles the decision is made easier. If it is concluded that any extraneous pigmented lesion is a freckle and not a seed there is no contraindication to local excision.

Additionally, granular pigment in the dependent part of the filtration angle is an almost constant finding in the presence of an iris melanoma and presents no contraindication to an excisional iridectomy. This fine pigment dust over the trabecula is not likely to be confused with tumor seeds which are larger and tend to grow over the iris surface. The latter are particularly marked in defuse malignant melanoma where their presence may verify the diagnosis in an early case where a slightly darker iris than that of the fellow eye is the only other finding.

4. *Absence of glaucoma.* Elevation of the intraocular pressure only in the involved eye implies that the filtration angle is involved and that the lesion is too extensive for local excision. This can almost always be verified by gonioscopic examination. In some such cases a ring melanoma may extend primarily around the ciliary body, manifested clinically as a localized extension into the iris. In diffuse malignant melanoma where the first apparent manifestation is an iris darker than its fellow, glaucoma ensues early due to the accumulation of pigment and tumor cells which can often be appreciated only by gonioscopy. Needless to say, in such instances local excision should not be done.

5. *Peripheral location.* When a suspected lesion is in the periphery of the iris closely approaching the angle area an iridectomy should be done; whereas, a similar lesion located near the pupillary area could be safely followed by further observation. The reason for this is that any additional growth in the periphery would involve extension into the angle, the ciliary body, or the cornea. An iridectomy in such cases might well obviate a later enucleation. It is possible to perform successful excision of a peripheral lesion in apposition to the cornea, providing there is no actual invasion of the cornea or angle structures.

6. *Excessive apprehension on the part of the patient.* Occasionally the concern of ophthalmologists over the status of a melanoma found on routine examination or discovered by the patient and necessitating continued observation leads to inordinate apprehension on the patient's part. Regardless of whether or not such a lesion requires removal by the usual criteria, it may be necessary to excise the lesion in order to reassure the patient completely enough to avoid serious emotional disturbance.

Technique of excision

The object of excisional iridectomy is to remove all of the tumor and to do so without causing dissemination of tumor cells in the eye or in the incision. In order to accomplish this it is essential to make a limbal incision large enough to permit excision of

Fig. 1 (Reese and Cleasby). A limbal section has been made to expose the tumor. Three sutures have been preplaced on the scleral side of the incision and a silk suture placed through the corneal side of the incision. The conjunctival flap is small and there is little shelving of the incision.

the lesion by basal iridectomy under direct visualization.

A conjunctival flap is dissected down to the limbus at the point where the tumor is located and sutures inserted in the manner of a cataract extraction. The conjunctival flap is easier to manipulate if it is kept very small.

Entry into the anterior chamber is usually made with a keratome to one side of the lesion so that the point does not disturb the tumor. The incision should be as far back as possible in order to approach the base of the iris and avoid shelving. The section is then enlarged to either side of the lesion. Usually somewhat less than a full 180 degrees provides sufficient exposure.

If there is much shelving of the incision, the periphery of the iris is concealed, making performance of basal iridectomy more difficult and preventing adequate view of the peripheral portion of the iris. A silk traction suture placed through the corneal margin of the incision aids in providing better visualization and allows wide separation of the wound lips when withdrawing the tumor from the eye (fig. 1). Further aid in inspecting the iris behind the tumor is provided by traction on the iris toward the pupillary area and retraction of the scleral margin of the incision by a limbal suture.

After trying various ways of performing the iridectomy, the best technique was found to consist of holding the pupillary margin to one side of the tumor and making a radial cut with the scissors to the base of the iris while exerting traction centrally (fig. 2). This is repeated on the opposite side of the tumor and the included iris tissue containing the lesion is torn from its insertion into the ciliary body (fig. 3). This latter step cannot be executed successfully unless both radial cuts extend to the extreme periphery.

Following removal the excised iris and tumor tissue has a marked tendency to curl up and become distorted. If the specimen is placed in fixative in this state, microscopic sections will be so distorted that it is difficult to study them adequately and often not possible to evaluate whether or not the tumor has been completely excised (fig. 4). Therefore, if some attention is given to the specimen after excision, it is very helpful to the pathology laboratory and the surgeon can obtain more accurate information from

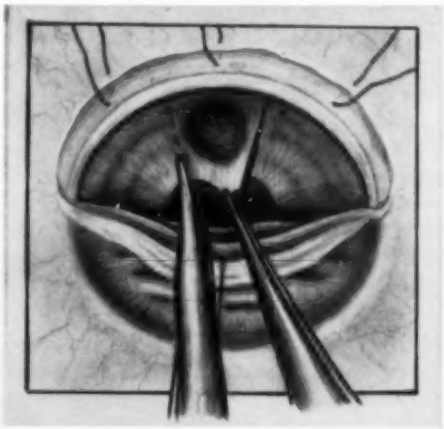

Fig. 2 (Reese and Cleasby). Traction is exerted centrally with a forceps while radial cuts are made on either side of the tumor from the pupillary margin to the base of the iris.

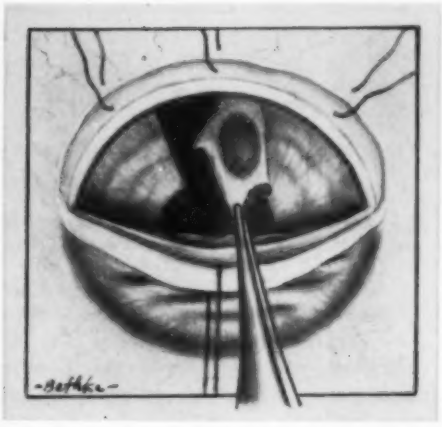

Fig. 3 (Reese and Cleasby). The portion of the iris containing the tumor between the two radial cuts is torn from its insertion into the ciliary body.

Fig. 5 (Reese and Cleasby). This shows the manner in which the excised specimen should be pinned out flat on the end of a tongue depressor prior to fixation in order to avoid distortion.

the pathologist. It is advisable, as advocated by Wadsworth, to pin the specimen carefully on the end of a tongue depressor prior to fixation (fig. 5). Radial section can then be made showing the full extent of the excised iris and tumor (fig. 6).

Enucleation

After the discussion of the criteria for excisional iridectomy, it is apparent that enucleation is indicated in the following situations:

1. When the tumor is not sufficiently localized for removal by iridectomy. This would be true when
   a. The tumor is of the diffuse type.
   b. A ring-type melanoma is present.
   c. The iris lesion involves the ciliary body. The presence of dilated episcleral vessels over the suspected region or local-

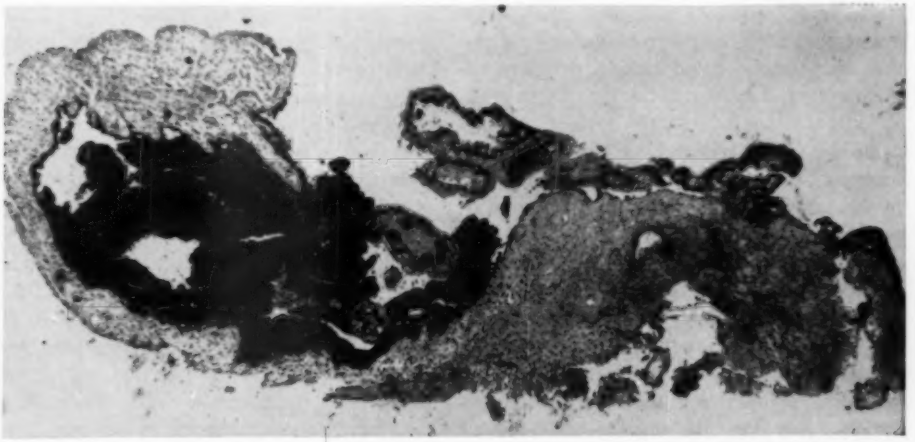

Fig. 4 (Reese and Cleasby). This is the appearance of an iris tumor removed by excisional iridectomy which was allowed to curl and become distorted prior to being placed in fixative. It is very difficult to evaluate the extent of the tumor and completeness of excision.

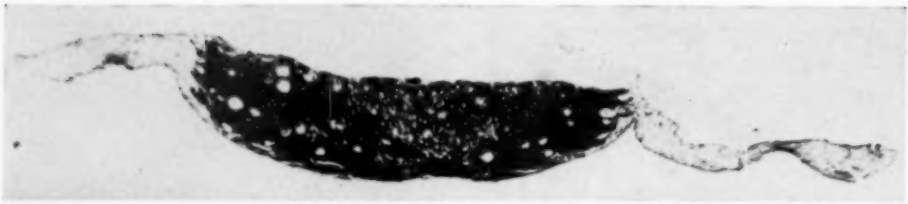

Fig. 6 (Reese and Cleasby). This is the appearance of a section prepared from a specimen handled in the manner shown in Figure 5. The relationship of iris and tumor tissue is well preserved and completeness of excision can be readily evaluated.

ized cataractous changes in that area may occasionally provide clinical evidence incriminating the ciliary body even when there is no tumor visible behind the iris through a dilated pupil.

d. Tumor seeds are spread over the iris or in the filtration angle.

e. The tumor invades the cornea.

f. Glaucoma is present only in the involved eye. As discussed previously, this indicates a sufficient encroachment on the filtration angle to contraindicate local excision.

2. When it is known that tumor tissue remains in the eye following iridectomy. This may be in the nature of microscopic and/or clinical evidence. If it is not possible to make a definite evaluation of the completeness of the excision on microscopic study, a diagnosis of malignant melanoma per se does not provide grounds for enucleation when there is no clinical evidence of remaining tumor.

In the recent report by Rones and Zimmerman,[1] there was evidence suggesting that in 11 cases in their series enucleation was performed following iridectomy solely because of a diagnosis of malignant melanoma on microscopic study and without any indication that the tumor had not been completely removed. Although we were unable to document similar cases in this series, it is worth emphasizing that the pathologist cannot bear alone the responsibility for all such decisions. In one of our cases an enucleated eye did prove to have no residual tumor when the distorted iridectomy specimen was reported microscopically to show incomplete removal.

Enucleation was performed subsequent to initial iridectomy in 10 patients in our group, and the above-mentioned case was the only one in which the enucleated eye did not contain residual tumor. However, there were six cases of primary enucleation in which it appeared that an iridectomy would have sufficed. Separating cases studied in the last 10 years from those studied previously, it is found that three of these latter six enucleations were performed prior to January 1, 1948, and three subsequent to that time. Of the total of 72 enucleations, 26 were performed prior to January 1, 1948, and 46 after that date. Thus we are unable to confirm the impression of Rones and Zimmerman,[1] and of Duke and Dunn[2] that there has been an increasing tendency to perform unnecessary enucleations in recent years.

Further analysis of the type of treatment employed within the past 10 years compared with that in previous years shows that there were 26 patients subjected to enucleation and 12 to iridectomy prior to January 1, 1948. Since that time there have been 46 enucleations and 49 iridectomies. In addition, most of the 22 patients who have been observed only were seen in the past 10 years. Thus, in this series, the trend has actually been to do proportionately fewer rather than more enucleations. Aside from the changing attitude of ophthalmic surgeons, another factor may be increased attention paid to early lesions by both the medical profession and the general public.

Observation

In view of the relatively low malignant potential and usually slow growth of the iris melanomas, observation is not to be condemned if the choice between surgery and observation is not clear. Discrete pigmented iris lesions of variable size and elevation are relatively common and frequently must be observed over a period of time to determine whether or not characteristics signifying malignant behavior are manifested. Undoubtedly many, if not all, malignant iris melanomas arise from benign lesions which in the beginning are usually small and rather flat but may develop considerable size and elevation. Lack of progression is the feature which establishes the diagnosis in the absence of other previously mentioned clinical criteria of malignancy.

Appraisal of the behavior of iris melanomas on the basis of present knowledge indicates that observation is the preferred course in some cases which formerly would have been candidates for surgery. This is particularly true of a localized tumor occupying a position far enough removed from the angle so that if growth is established an iridectomy would probably suffice instead of an enucleation. The progression of a similar growth in the angle would probably call for an enucleation. In deciding on the best course to pursue for any given lesion it is well to keep in mind the age of the patient and his life expectancy, especially in situations where enucleation of an eye with good vision is being considered.

It is not possible at present to state whether or not there is increased risk in pursuing a course of observation in young women who are pregnant or likely to become so. Melanomas in general are thought to be activated occasionally by pregnancy[3, 4] but there was only one instance in this series in which pregnancy may have had a bearing on the behavior of the lesion. This was a case in which a melanoma of the iris gave rise to a hyphema.

Similarly, it is thought that puberty may have an activating influence on melanomas.[5–7] Four of the tumors in this series occurred in prepubertal children, but there is only one case in which a patient was followed continuously through puberty by the same observer with specific attention to the lesion. This patient was 10 years of age when the tumor was discovered. It was followed until she was 16 at which time the clinical behavior prompted an excisional biopsy. Histologic study indicated that the tumor was a malignant melanoma, completely excised.

TABLE 1

DISTRIBUTION OF CASES WITH FOLLOW-UP INFORMATION

Therapy	Follow-Up (yr.)	Number
Enucleation	Over 20	2
	15–20	3
	10–15	8
	5–10	20
	1– 5	25
	0– 1	11
TOTAL		69
Iridectomy	Over 20	1
	15–20	2
	10–15	2
	5–10	15
	1– 5	24
	0– 1	5
TOTAL		49
Observation	15–20	1
	10–15	1
	5–10	5
	1– 5	10
	0– 1	5
TOTAL		22

Prognosis

The over-all mortality in this series, as in other groups reported, is quite low.[1, 2, 8–10] There have been four known deaths due to metastatic spread in the 140 cases with follow-up information. This is a mortality rate of three percent. Table 1 shows the distribution of cases for which follow-up information is available. Altogether 60 cases have been followed for five years or longer

and 120 cases for two years or longer.

Of great importance is the fact that no deaths occurred in patients receiving excisional iridectomy as the definitive therapy. It is evident that an iridectomy performed properly at a time when all the tumor can be removed in this manner not only prevents metastastic involvement but avoids the late complications of secondary glaucoma, pain, and blindness which can result from local dissemination.

Analysis of the four fatal cases shows that enucleation was ultimately performed in each instance. In all cases microscopic study revealed that tumor had spread beyond the reach of local excision. In two cases excisional biopsies were performed six days and one week prior to subsequent enucleation, respectively. In a third case, iridectomies were performed in the course of two trephining operations during a five-month period prior to enucleation when it was ultimately recognized that the glaucoma present was secondary to a diffuse melanoma of the iris. In the fourth case enucleation was performed without initial iridectomy. Interestingly, three of these four cases were the diffuse type of melanoma in which delay is more likely due to failure to recognize the true nature of the process. The other case was a more localized lesion but with extension beyond the iris. In this latter case iridectomy had been performed initially, although by the previously mentioned criteria it should not have been done.

It cannot be definitely proved, of course, that surgical interference in three of the four fatal cases prior to enucleation contributed to the ultimate outcome. It does seem obvious that the surgeon should proceed directly to enucleation if there is clear-out evidence that local excision will not remove all the tumor.

There have been no progressive changes reported in the patients followed by observation only. However, a number of patients were followed for a period of years before finally coming to surgery and thus being eliminated from the observation group. One of the patients in this latter situation had been seen and observation advised 13 years prior to enucleation. This patient did not report for periodic examination in the interim as recommended and it is quite possible that an iridectomy performed earlier could have saved the eye. He is reported to have died two and a half years later of probable metastases, but this could not be verified well enough to list his case as a tumor death.

An unusual case reported by Koenig[11] serves to illustrate the unpredictability of these tumors. A large melanoma involving the iris and ciliary body in a patient's only eye was followed over a period of 20 years, and by history a lesion had been present at least 30 years earlier. No secondary complications or metastases developed and the eye was obtained at autopsy following death from unrelated causes.

Since the great majority of patients remaining in the observation category have been followed less than 10 years, it may be some time before the final prognosis of this group is known.

In view of the relatively slow growth of iris melanomas in general and the fact that metastases from other ocular melanomas can appear up to 20 or more years after appreciation of the primary lesion, further long-term follow-up studies are definitely in order for all patients found to have iris melanoma.

Summary

Any pigmented iris lesion showing progressive growth or other evidence of malignant behavior should be excised by means of iridectomy if it seems possible to remove it completely in this manner. A lesion located in the periphery of the iris should be excised early, since any growth would be likely to involve the angle and ciliary body.

Enucleation is advisable if the tumor has obviously spread beyond the reach of local excision or there is evidence of residual

tumor peripheral to a previously performed iridectomy. The pathologic diagnosis of malignant melanoma does not provide grounds for enucleation in the absence of microscopic and/or clinical evidence of remaining tumor.

Observation is necessary in any case in which there is not clear-cut evidence of malignant character or behavior and there are no other indications for surgery.

The over-all mortality in this series, as in other groups reported, is quite low. Of great importance is the fact that none of the deaths occurred in patients in which local excision proved to be definitive on the basis of clinical and microscopic evidence. There have been four known deaths in this series due to metastatic spread in the 140 cases with follow-up information. Enucleation had been performed in the four fatal cases, three following earlier iridectomy. In each instance tumor had spread beyond the reach of local excision.

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PENETRATING AUTOKERATOPLASTY OF ENTIRE CORNEA*

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The concept that homografted tissues, other than the cornea and cartilage, illicit and are destroyed by an allergic reaction of the host has been repeatedly established in experimental studies.[1-3] Evidence has also been presented that corneal homografts may participate in a similar reaction.[4-7] Some ophthalmologists have accepted this explanation as the cause of delayed opacification of corneal grafts,[7-9] others have been less enthusiastic about this idea.[10-15] Thus, in the reports of the latter they have either made no mention of the donor-recipient reaction as a cause of opacification of grafts or they have made only a cursory statement to the effect that an allergic response of some type might have been involved in the delayed clouding.

The following five cases of autologous penetrating transplants of the entire cornea are reported, first to lend support to the theory that homologous grafts are damaged by an allergic response of the host and second to recall that an eye with a complete opacity of the cornea but with functioning

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retina can be saved by an autologous corneal graft.

Case reports

Case 1* (V.M., J.H.H. 729772)

This patient was aged 62 years, a white man whose general medical history revealed that he had hypertension for the past 20 years with a systolic blood pressure ranging in the neighborhood of 220 mm. Hg. For the past year he had been on antihypertensive drugs which reduced his systolic pressure to 160 mm. Hg. Two years prior to admission the patient had had a mild right hemiplegia which had cleared without residual symptoms. General physical examination revealed that his blood pressure was 160/100 mm. Hg., pulse 72. His heart was found to be within normal limits by percussion. The heart rhythm and sounds were normal. His neurologic examination was essentially normal except for hyperactive reflexes and an absence of Babinski or Hoffman reactions on the right side.

His ocular history revealed that he had had no ocular difficulty until April 23, 1951, at which time he had a sudden complete loss of vision in the right eye as a result of a thrombosis of the central retinal vein. Examination of the left eye, at that time, revealed that he had an advanced glaucoma with an ocular tension of 64 mm. Hg. The tension in the right eye was controlled by a cyclodiathermy. In the left eye the pressure was partially controlled with medical therapy. By March 6, 1952, the tension could no longer be controlled in the left eye with medical therapy. An iridencleisis was therefore done. This was followed by a massive postoperative anterior chamber hemorrhage. An attempt was made to irrigate the blood out of the anterior chamber but this resulted in a traumatic cataract. On August 27, 1952, an extracapsular cataract extraction was done. This was again followed by a delayed massive anterior chamber hemorrhage. The blood gradually cleared from the anterior chamber but the patient was left with peripheral anterior synechias and a bullous keratopathy which caused a marked reduction in visual acuity. In January, 1955, an eight-mm. penetrating homologous corneal graft was done on the left eye. The graft remained clear for approximately two months and the patient obtained 20/200 vision. The ocular tension was controlled within normal limits by the use of di-isopropylfluorophosphate (DFP).

When the patient was first seen at The Johns Hopkins Hospital on February 14, 1956, his visual acuity in the right eye was no light perception and the left eye could not be corrected above 1/200. Light perception was excellent.

In the right eye the cornea was crystal clear. The anterior chamber was somewhat shallow. The iris was atrophic above and the pupil was drawn upward. There was no evidence of iris rubeosis. The lens was cataractous. The tension measured 2/5.5 or 29 mm. Hg (Schiøtz).

In the left eye there was an opaque corneal graft with marked bullous keratopathy. The periphery of the cornea was relatively clear. The anterior chamber was quite shallow and the iris was adherent to the wound edges of the graft in many areas. The tension measured 3/5.5 or 24 mm. Hg (Schiøtz).

The patient was diagnosed as having a blind eye on the right side as the result of an old thrombosis of the central retinal vein. His glaucoma in this eye had been controlled by a cyclodiathermy. In the left eye he had a history of glaucoma with advanced glaucomatous atrophy, operative aphakia, an opaque corneal graft, and bullous keratopathy. It was thought that his chances of obtaining a clear transplant from a homograft were extremely slight. It was also decided that a penetrating graft of his entire cornea was indicated because of his advanced bullous keratopathy.

On February 15, 1956, the right eye was enucleated. An 11-mm. circular penetrating graft was taken from this eye and placed in the left eye. The donor graft was sutured in place with interrupted corneal-to-scleral 6-0 black silk sutures. A complete iridectomy was done and formed vitreous was lost at the time of the operative procedure. At the end of the operation a large bubble of air was placed in the anterior chamber sufficient to raise the ocular tension to approximately 30 mm. Hg. The corneal wound showed no evidence of leakage.

The postoperative course was relatively uneventful except for a moderate striate keratopathy in the graft. There was no anterior chamber hemorrhage. The corneal-scleral sutures were removed at the end of three weeks. By March 16, 1956, about four weeks after operation, he was able to read 20/100 with the aid of the following lens: +11.0D. sph. ⊃ +1.0D cyl. ax. 30° (fig. 1). The patient was discharged from The Johns Hopkins Hospital and returned to California where he was followed by Dr. Virgil C. Snow.

On April 5, 1956, his visual acuity was correctible to 20/70. With the use of Diamox and pilocarpine his tension measured 24 mm. Hg. (Schiøtz), in spite of the use of 0.25-percent DFP twice a day and 250 mg. of Diamox twice a day. In September, 1956, a cyclodiathermy was done to control his ocular tension. The visual acuity was reduced to 20/100. From this time until the patient's death from cardiovascular disease in April, 1958, the cornea remained entirely clear. His visual acuity, however, was gradually reduced, either from his advanced glaucoma or vascular disease, to hand motions.

The eye was obtained for histologic study at autopsy. The corneal endothelium, epithelium, and stroma were entirely within normal limits. No abnormal blood vessels were seen in the periphery of the cornea. The area of Schlemm's canal had been completely obliterated by the operative procedure. There was a defect of the internal surface of the wound in most areas and in some regions the root of the iris and ciliary processes were in-

*This case is reported by the kind permission of Dr. Virgil C. Snow, Fresno, California.

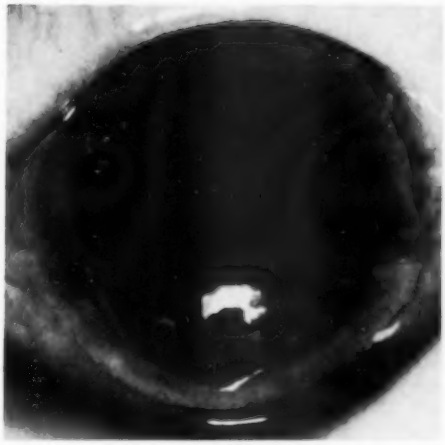

Fig. 1 (Maumenee). *Case 1.* V. M. Clear 11-mm. penetrating corneal autograft four weeks after operation.

corporated in this defect. The ciliary body was quite atrophic and the ganglion cells of the retina were markedly reduced. There was considerable glial proliferation and atrophy of the optic nerve.

CASE 2 (L. S.)

This 56-year-old white man was first seen in consultation at the Stanford University Hospital on December 2, 1952. At that time he gave a history of having a very labile blood pressure that became elevated to approximately 220 mm. Hg, on occasions.

In 1918, the patient had suffered an accident to his left eye with the resultant loss of central visual acuity. In 1942, he was discovered to have glaucoma in both eyes and was placed on miotics. From approximately 1947 until 1952, the tension in both eyes was extremely variable. Frequently it was recorded as high as 90 mm. Hg (Schiøtz). However, at other times it was entirely within normal limits. Because of the fact that the patient had persistently good vision and relatively little loss of visual field, he was followed on miotic therapy.

When the patient was first seen on December 2, 1952, his corrected visual acuity in the right eye was 20/15 and in the left eye light perception with poor projection. The visual field in the right eye with a 4/2,000 white test object was reduced to about five degrees. With a 10/2,000 white test object there was an early Bjerrum scotoma and a baring of the blindspot. The tension in the right eye measured 49 mm. Hg (Schiøtz) and the left eye was too high to be recorded. Gonioscopic examination revealed that the angle of the anterior chamber was almost completely closed. The iris either touched the trabecular region in most areas or was so close to it that only a questionable cleft could be seen. Tonography revealed the facility of aqueous outflow in the right eye was 0.13 and the left eye 0.05. Under sedation and miotics the patient's tension fell to 18 mm. Hg (Schiøtz). The depth of the anterior chamber measured approximately 1.5 mm.

A diagnosis of chronic angle-closure glaucoma was made in the right eye. It was thought that, since the tension could be reduced to a relatively normal level and because the facility of outflow was within questionable limits, an iridectomy should be performed on the right eye.

A diagnosis in the left eye was made of absolute glaucoma with macula scarring from an old injury.

In December, 1952, an iridectomy was done on the right eye under general anesthesia. The patient developed a malignant glaucoma but the lens was not removed for several days because the patient's internist did not think he was in condition to undergo anesthesia. Following the cataract extraction the anterior chamber remained quite shallow and the patient's cornea became completely edematous. The tension in the right eye became elevated to 56 mm. Hg by February 26, 1953.

Between April, 1953, and April, 1956, the patient required seven cyclodiathermies to control the tension in his right eye. During this time he was also placed on Diamox and miotics. By June, 1956, the patient still had good light perception in his right eye but his projection was faulty and his entoptic imagery was absent. It was thought that his left eye was entering phthisis; therefore, in July, 1956, a 10-mm. autocorneal transplant was done. After removing the left eye, the cornea was sutured in place by direct corneal-to-scleral sutures.

The patient's postoperative course was amazingly uneventful. The graft remained entirely clear during the entire postoperative period. By September 11, 1956, his tension was found to be 20 mm. Hg (Schiøtz) and his visual acuity was limited to counting fingers. By February 4, 1957, the patient's visual acuity had increased to 20/50, his tension measured 18 mm. Hg, but his visual field was limited to about five degrees with a 10/2,000 white test object.

The patient's visual acuity has varied between 20/50 and 20/30 up until the present time (fig. 2). His tension has remained within normal limits and his facility of outflow has been about 0.14 to 0.20. The optic nerve shows advanced glaucomatous cupping.

CASE 3 (S. R.—J.H.H. 767778)

This patient was a 61-year-old white man who was first seen in the Wilmer Institute of The Johns Hopkins Hospital on December 12, 1956. His family history and general medical history were noncontributory.

The patient was first found to have glaucoma in his left eye in June, 1948. At that time the visual acuity in his right eye was 20/20. Tension measured 5/5.5 or 17 mm. Hg (Schiøtz). In the left eye the visual acuity was 20/70. The tension measured 2/10 or 59 mm. Hg (Schiøtz). The visual field

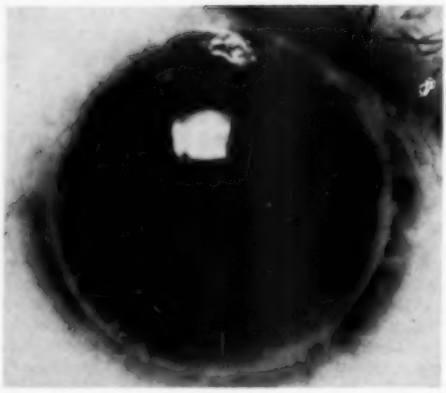

Fig. 2 (Maumenee). *Case 2.* L. S. Clear 10-mm. penetrating corneal autograft two and one half years after operation.

in the right eye was entirely normal; in the left there was a complete loss of the upper nasal quadrant to the point of fixation.

On June 17, 1948, an iris inclusion operation was done on the left eye. The postoperative course was uneventful except for a flat anterior chamber which was reformed on the fourth day by air injection.

The tension in both eyes was controlled with 0.5-percent Carcholin to each eye twice a day until March 16, 1956. At that time the pressure was found to be 1/5.5 or 34 mm. Hg (Schiøtz) in each eye. Diamox therapy was instituted.

When the patient was first seen in consultation on December 12, 1956, he was taking 500 mg. of Diamox twice a day and 0.25-percent Florpryl (DFP) once a day.

The visual acuity in the right eye was correctible to 20/25. The tension measured 4/7.5 or 30 mm. Hg (Schiøtz). The visual field in this eye to a 3/1,000 white test object showed a definite early Bjerrum field defect. Peripheral visual field to a 3/330 white test object was entirely within normal limits. Gonioscopic examination revealed a very shallow angle with peripheral anterior synechias covering the trabecular area in many regions. The depth of the anterior chamber measured about 2.3 mm. The lens was clear. The fundus appeared entirely normal.

In the left eye the visual acuity was correctible to counting fingers at three feet. The tension measured 8/7.5 or 15 mm. Hg (Schiøtz). The visual field was limited to approximately one degree with a 6/330 white test object. There was a functioning iridencleisis above with a good conjunctival bleb. Gonioscopic examination revealed that the angle was practically obliterated except in the area of the iridencleisis. On ophthalmoscopic examination there was a nuclear cataract but the fundus could be seen fairly well and the patient had advanced glaucomatous cupping with the vessels pushed far to the nasal side. It was felt that his visual acuity of counting fingers at three feet was due to his optic atrophy from glaucoma rather than his cataract.

The patient was diagnosed as having bilateral angle-closure glaucoma with superimposed open-angle glaucoma in the right eye and a functioning iridencleisis in the left eye. It was advised that, since the patient's tension could not be controlled with medical therapy and since there was a definite early visual field defect in the right eye, an iridencleisis be done on this side.

A Lagrange sclerectomy was done on December 14, 1956. The patient was seen again in consultation on February 1, 1957, at which time his visual acuity could be corrected to 20/400. The lens was included in the Lagrange sclerectomy above. The iris touched the posterior surface of the cornea everywhere and the tension measured 1/10 or 69 mm. Hg (Schiøtz). It was advised that an intracapsular cataract extraction be done on the right eye.

On February 2, 1957, a linear incision was made in the cornea above and an extracapsular cataract extraction was done. This reportedly reduced the patient's tension for a few days, but when he was seen again on November 29, 1957, the anterior chamber was completely obliterated. There was considerable cortical material behind the iris and in the pupillary area. The anterior chamber was completely flat. Visual acuity was limited to hand motions and his tension measured 1.5/10 or 64 mm. Hg (Schiøtz) in spite of the use of 500 mg. of Diamox four times a day and neosynephrine (one percent) to his eye twice a day. The patient's cornea was about twice the normal thickness above and numerous bullae were present in the epithelium.

On March 29, 1957, a lavage and capsulotomy was done on the right eye. The postoperative course was complicated by considerable bleeding into the anterior chamber and vitreous. The tension, however, remained in the neighborhood of 20 to 27 mm. Hg (Schiøtz) until April 12th, at which time it rose to 31 mm. Hg and, by April 16th, it was elevated to 61 mm. Hg (Schiøtz). For this reason, on April 16, 1957, a cyclodiathermy was done on the right eye.

Following this last operation his tension remained controlled in the neighborhood of 12 mm. Hg (Schiøtz) and his visual acuity gradually improved to 10/400. The cornea was quite edematous and there was still considerable blood in the vitreous. The patient's tension became elevated again and 500 mg. of Diamox a day was required to control his pressure. By June 12, 1957, the pressure could no longer be controlled by medical therapy and a cyclodiathermy was done over the lower half of his globe. Again the pressure was controlled for a short while, but on July 3rd, his pressure again became elevated and he was placed on 500 mg. Diamox twice a day. The tension remained controlled on medical therapy but, because of the increasing corneal edema, his visual acuity was reduced to about 5/200.

By February, 1958, it was decided that there was very little chance of the cornea of the right eye clearing and, for this reason, on February 24, 1958, an enucleation was done on the left eye and a 10-mm. penetrating autocorneal graft was done on the right side. At the time of this operative procedure, no formed vitreous was lost through the anterior part of the wound but one-half cc. of fluid vitreous was aspirated from the midportion of the vitreous to allow the hyaloid face to drop back. The iris which was adherent to the recipient button of cornea was removed close to its insertion into the ciliary body. The donor corneal button was sutured in place with approximately 17 7-0 black silk sutures and a large bubble of air was placed behind the cornea, separating the vitreous from the posterior surface of the cornea.

The postoperative course was relatively uncomplicated. By March 18th the patient had 20/70 vision and with the use of Diamox (500 mg. twice a day) and pilocarpine (four percent, three times a day) his ocular tension measured 4/5.5 or 20 mm. Hg (Schiøtz). At no time was there any clouding of the corneal graft and by March 24, 1958, he was able to see 20/50. His visual acuity from that time until the present has varied between 20/50 and 20/60. His intraocular pressure has varied between 2/5.5 and 7/5.5 or 29 mm. Hg and 12 mm. Hg (Schiøtz). Applanation tonometry on July 2, 1958, showed that the patient's scleral rigidity was normal. His facility of aqueous outflow was 0.10 and the tension on this day measured 24 mm. Hg with both applanation and Schiøtz tonometer. Tonometry was repeated again on August 5, 1958, at which time the facility of outflow was 0.08 and the tension measured 12 mm. Hg with both the Schiøtz and applanation tonometer.

The patient's corneal graft is crystal clear (fig. 3). The fundus can be seen in detail. Unfortunately there is a glial membrane that extends from the surface of the disc across to the macular area. This macular lesion accounts for his visual acuity of 20/50. His visual field to a 9/2,000 white test object comes to within five degrees of fixation above, 10 degrees nasally, 25 degrees below, and 25 degrees temporally. Gonioscopic examination reveals that the incision for the corneal graft has almost completely obliterated Schlemm's canal. The iris has been removed from the root of the ciliary body in most areas, but in some few areas a small tag of iris remains. Tension is controlled at the present time with the use of 250 mg. of Diamox twice a day and epinephrine bitartrate (two percent) two drops to the right eye twice a day.

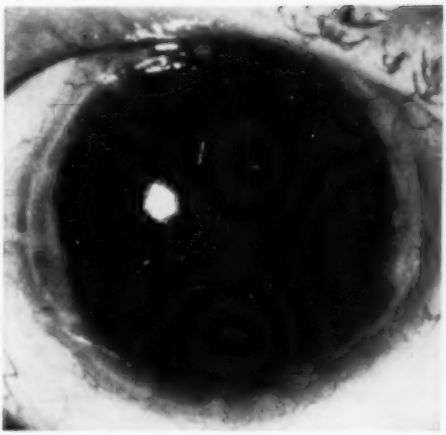

Fig. 3 (Maumenee). *Case 3.* S. R. Clear 10-mm. penetrating corneal autograft one year after operation.

CASE 4* (W. O'D.—J.H.H. 787380)

This 19-year-old white man was first seen at the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital on October 4, 1957. The patient's family history is of interest in that his mother developed a mature cataract at the age of 22 years because of chronic uveitis. The patient's past medical history is of interest in that he had rheumatic fever at the age of two and a half years. He had no other history of rheumatoid disease.

In 1938, at the age of seven years, the patient developed a bilateral uveitis. At the age of nine years he suffered a massive intraocular hemorrhage in the right eye which reduced his visual acuity on this side to no light perception. By 1957, at the age of 19 years, his uveitis was entirely quiescent in the left eye but his visual acuity was reduced to 20/200 because of an immature cataract.

On June 14, 1957, an extracapsular cataract extraction was performed at which time there was a loss of vitreous. By June 29th, his visual acuity was correctible to 20/60 and by July 24th, it had improved to 20/40. The patient had a shelving corneal section with some vitreous adherent to the back of the cornea. An epithelial downgrowth was looked for but none was seen. By September 5th, his visual acuity was reduced to 20/70 because of capsular remains. On September 19, 1957, a discission of the capsular remains was done and was followed by an anterior chamber hemorrhage. On October 2nd, a membrane was noted over the temporal pillar of the iris which was thought to represent an epithelial downgrowth.

When the patient was first seen in consultation on October 4, 1957, he had a moderate photophobia. On examination of the right eye he had a crystal clear cornea, an iris bombé, and a mature cataract. The iris appeared to obliterate the angle everywhere in the periphery. His tension measured 2/10 or 59 mm. Hg (Schiøtz). The vision in the right eye was limited to light perception and poor projection.

In the left eye there was marked photophobia and a mild circumcorneal congestion of the blood ves-

* This case is reported by the kind permission of Dr. Alston Callahan of Birmingham, Alabama.

sels. The corneal section was shelved and a membrane covered the entire temporal half of the iris extending from about the 1 o'clock to 6:30-o'clock position. On the nasal side at the 11 o'clock position, the iris was adherent to the back of the cornea and a membrane also covered this side of the iris. The only area which appeared to be free of epithelial downgrowth was a small region between the 6:30- and 9-o'clock position. The central portion of the cornea was clear but there was a fairly heavy pupillary membrane. The tension measured 2/5.5 or 29 mm. Hg (Schiøtz). Visual acuity was limited to hand motions and excellent light perception.

It was thought that the patient had an old uveitis with an intraocular hemorrhage in the right eye and subsequent retinal detachment. In the left eye he had had a cataract extraction with a secondary pupillary membrane and epithelial downgrowth which involved almost all of the angle of his anterior chamber. The patient was advised to enter the hospital for an attempted removal of the epithelial downgrowth from his anterior chamber but he refused to have the operation done.

He was not seen again until February 12, 1958, at which time he returned because his left eye had become quite painful. At that time it was noted that the epithelial downgrowth had extended farther across to the central portion of his cornea and that there were now numerous keratic deposits on the posterior surface of the cornea.

It was felt that this case was almost hopeless and that the only possible chance of saving any visual acuity for this patient was to remove the entire left cornea with a rim of two or three mm. of sclera and, at the same time, to remove as much of the epithelial downgrowth as possible after the eye had been completely opened.

On February 13, 1958, the right eye was enucleated. A Flieringa-Bonaccolto ring was sutured to the anterior segment of the sclera of the left eye and a 13.5 mm. corneal-scleral graft was obtained from the right eye and transferred to a similar area of the left eye. An attempt was made to remove all of the patient's iris and as much of the epithelial downgrowth from the anterior face of the vitreous, capsular remains, and ciliary body as possible. Fluid vitreous was taken from the center of the vitreous but, in spite of this, a small amount of formed vitreous was lost during the operative procedure. There was some bleeding from the ciliary body into the vitreous during the operation. The donor sclera was sutured to the recipient sclera and a pursestring conjunctival flap was pulled over the donor-recipient junction. Just prior to closing this flap the anterior chamber was filled with a large bubble of air.

During the postoperative course the patient was kept flat in bed so that the vitreous would not come in contact with the back of the cornea.

The cornea showed very little reaction during the entire postoperative period and remained entirely clear. The blood in the patient's vitreous, however, allowed only a dull reflex to be obtained. His visual acuity was limited to counting fingers.

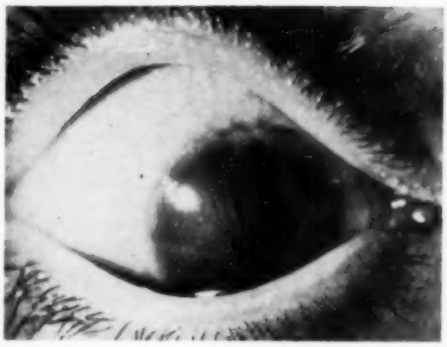

Fig. 4 (Maumenee). *Case 5—Barraquer.* Corneal clouding following cataract extraction, February 9, 1955.

Dr. Callahan reported that the patient's tension remained within normal limits without the use of medical therapy. By August 26, 1958, his visual acuity had increased to 20/200 with a +16.0 D. sph. ⊖+1.25 D. cyl. ax. 75°. The hemorrhage in his vitreous was gradually clearing. On October 18, 1958, he developed a retinal detachment. His cornea remained entirely clear but he refused further surgical treatment for his eye.

It is interesting that this patient had had no evidence of recurrence of his epithelial downgrowth, although the follow-up period on him has been relatively short.

CASE 5 (M.V.)

This 14-year-old white girl was a patient of Dr. Joaquin Barraquer of Barcelona, Spain, and her history is being reported through the kind permission of Dr. Barraquer.

The patient had a cataract in her right eye which reduced her visual acuity below useful level. In the left eye she was essentially blind from an old iridocyclitis. In January, 1955, a cataract extraction was done on the right side. Following this

Fig. 5 (Maumenee). *Case 5—Barraquer.* Clouded homograft, January 23, 1957.

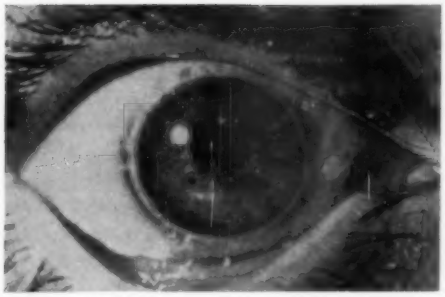

Fig. 6 (Maumenee). *Case 5—Barraquer.* Clear autograft, May 9, 1958.

the patient developed a corneal dystrophy and her visual acuity was reduced to hand motions. In April, 1955, a four-mm. lamellar corneal graft was done. This did not improve her visual acuity. In February, 1956, an eight-mm. lamellar corneal transplant was done but again her visual acuity was not improved. In January, 1957, the patient's visual acuity in the right eye was still limited to light perception. The cornea was markedly edematous and vascularized. At this time a 10-mm. autocorneal graft was taken from the patient's left eye and inserted into the right eye. The graft was held in place by direct corneal-to-corneal sutures. A similar sized corneal homograft was inserted into the left eye.

Thirty-four days after operation the visual acuity in the right eye was 4/200. Forty-four days after operation it was 16/200. The visual acuity in the right eye gradually increased and by May, 1958, was 20/20.

The tension in the right eye immediately after operation remained within normal limits. By April, 1956, however, it had become elevated to 55 mm. Hg. A cyclodiathermy was done at that time. Since this operative procedure the tension has remained within normal limits.

The corneal homograft in the left eye became completely opaque.

Discussion

These five cases have been reported in great detail because of their extremely complicated histories. In none of the five cases would even the most optimistic of surgeons have offered better than a five to 10 percent chance of obtaining a clear corneal homograft. The size of the penetrating autografts varied from 10 to 13.5 mm. in diameter. In each instance the donor tissue was sutured directly into an extremely vascularized area of the recipient. In none of these patients at any time after operation was there the slightest evidence of a delayed opacification of the graft.

The observation that autologous keratoplasty gives better results than homologous grafts is not a new one. Early in this century Morax,[16] Plange,[17] Salzer,[18] and many others noted the superiority of autologous over homologous tissue. Friede[19] noted that 77 percent of his 17 rotating penetrating autologous keratoplasties remained transparent and 17 percent translucent, whereas only 32 percent of his homologous grafts remained transparent and 26 percent translucent. He observed that the delayed opacification of the graft did not occur with autologous material. In spite of the fact that several workers have mentioned the differences in response to autologous and homologous tissue, this point has not been adequately emphasized as an argument that the delayed clouding of the graft is due to the immune reaction of the host.

In recent years much has been learned about the immune reaction of the host to homologous tissue. This may be outlined as follows:

1. It is an acquired response to transplanted tissue.

2. The rate at which the initial immune response develops is dependent to a slight degree on the amount of tissue (dose of antigen) transplanted. An 0.5-mm. piece of Harderian gland, however, contains sufficient cells to illicit a reaction.[20]

3. The reaction is a systemic one, for a graft to any part of an animal will cause a transplant to any other part of the body to be destroyed at an accelerated rate.

4. A nonvascularized graft cannot initiate an immune reaction, but if the animal acquires an immunity from a vascularized second graft from the same donor then the initial avascular graft will be destroyed.[20-22]

5. The immune state cannot be passively transferred by serum transfusion but it can be established in a second animal by the transplantation of a lymph node or lymphocytes from an immune animal to a normal one of the same inbred strain.

6. The antibody is contained in lymphocytes of the immune host but not in the serum.

7. The immune lymphocytes must come into contact with the donor cells before destruction of the transplanted cells will occur.

Medawar[23, 24] has shown that the immune response is intimately bound to the genetic relationship of the donor and recipient. Thus tissue may be transplanted from one identical twin to another or from one animal to another in highly inbred strains. The transfer of nucleated cells from one animal to another when they are less closely related will illicit the reaction. The intensity of the response is dependent on the genetic similarity of the animal. Thus, a piece of skin that will survive only 12 days when transferred from one completely unrelated animal to another will live for over 100 days when transferred from the parent to one of the F_1 progeny of two highly inbred strains. The relation of the antigen to the chromosomes is further established by the fact that all cells of an animal contain all of the antigens that produce the immune response. Finally the antigen in the cell is destroyed by such mild methods of killing the cells as freezing and thawing, lyophilization and heating to 48.5°C. for 20 minutes. It can be preserved if the cells are destroyed by ultrasonic vibrations. The antigen is then found in the nucleus of the cell.

The immune reaction to homografts should not be confused with organ-specific sensitivity, such as occurs to lens, kidney, or spinal cord. In the former, the antigens are found in all of the tissues of one donor and are specific for that donor. In the latter, the antigens are found in many unrelated species but are specific for one organ.

Likewise it has been shown that antigens responsible for tissue transplantation immunity are not the same as those for blood groups.[23, 24] It differs from the transfusion incompatibility due to the ABO blood groups in that the antibodies in this response are either innate or are acquired early in life while those of tissue immunity occur only after the transplantation of tissue from a specific donor.

Homologous corneal grafts are successful because they are placed in an avascular bed and thus cannot illicit the immune reaction. Occasionally the rule is violated in a penetrating graft to an avascular cornea because the donor endothelium may become detached and carried by the aqueous to blood vessels of the host. These cells may then illicit the immune reaction.

The stromal cells are probably sufficient in number to illicit an immune reaction but the wide separation of the cells by the stromal ground substance isolates them so that they are poor stimulators of the reaction. Homotransplants of cartilage are also poor stimulators of this reaction because of the wide separation of the cells by the ground substance. Thus the avascularity of the recipient bed and the separation of the stromal cells by the ground substance places corneal grafts in a privileged position as far as the homograft reaction is concerned.

However, if a graft is placed in a vascularized cornea it will both illicit and respond to immune response. Penetrating grafts respond more readily to this reaction than do lamellar grafts.[25] Slight damage to the endothelium in a penetrating graft produces a marked edema of the graft while injury to a few stromal cells in a lamellar transplant may go unnoticed.

The failure of autologous penetrating grafts to develop a delayed clouding when placed in a vascularized bed is further evidence that this reaction by homologous tissue is a manifestation of the immune response to the host. This observation brings corneal grafts into closer relation to grafts of other tissue for it has long been known that transplantation of such tissues as skin, arteries, glands, and so forth, survive more readily following autotransplantation than they do homologous transplantation. It also suggests that if the antigens in the homografts could be eliminated, the value of keratoplasty would be greatly extended. Successful total grafts could then be obtained in almost any

eye with a good posterior segment.

The second reason for reporting these five cases of autologous transplantation of the entire cornea is that they should serve as a reminder that no matter how opaque, vascularized, or edematous the stroma of the recipient cornea may be a successful graft can be obtained from autologous transplantation of the cornea of the fellow eye. The circumstances under which this may be possible are obviously limited. However, in those instances where the patient is blind in one eye from retinal detachment, optic atrophy, or other change in the posterior segment and has a normal cornea on that side, and where the other eye is limited to light perception and good projection from corneal damage, this person is a good candidate for a corneal autograft.

Summary

Five cases of penetrating autologous transplantation of the entire cornea have been reported. These cases of successful transplantation have been cited as evidence that the delayed clouding of homologous corneal transplants is due to the immune reaction of the host. Further, these cases are reported to serve as a reminder that successful grafts can be obtained from autologous material when the chances of obtaining such results with homologous material would be almost zero.

The Johns Hopkins Hospital (5).

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RESEARCHES INTO THE REGIONAL DISTRIBUTION OF EYE DISEASE

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This paper is a plea for interest in a branch of ophthalmology which, being time-consuming rather than highly technical, has not yet attracted many workers, but which, from certain ecologic considerations, must be pursued at the present time, since the basic conditions for its success are fast disappearing from the world. I refer to a study of the natural incidence of eye disease in races and cultures different from our own, carried out before their contacts with our way of life have brought them into a similar environment and have modified the original pattern of their existence.

Work, as you know, has already been done along these lines in India, Africa, China, and Japan, but these areas have long been subjected to the impact of various cultures and enjoy widespread opportunities for travel. They are no longer entirely isolated and living to a uniform pattern.

On the other hand, much work has been done on the regional distribution of disease in our own countries, as between rural, urban, and industrial communities. This indeed formed the subject of a discussion opened by Mr. Jameson Evans at the 1957 meeting of the Australian Ophthalmological Society.

There remain, however, many relatively unopened areas of the world where rigid adherence to a traditional pattern of life still provides a uniform background of race, diet, climate, work, and social and marriage customs against which the local disease pattern can be studied. The problem is a difficult and fascinating one, and for a real comprehension of the geographic, cultural, and other factors responsible for the varying incidences of ocular disease we would have to correlate the findings of anthropologists, nutritional experts, microbiologists, entomologists, biochemists, and geophysicists, with possibly a few ecologists and some physicians thrown in for added good measure.

It is an heroic task but one which would well repay time spent on it. Without such a co-ordinated study we may well fall into error and it is possible that we shall miss scientific pointers of great significance.

I could instance here a reference to another field of research with which, as you know, I have had some contact. In the early 1900's it was widely believed that cancer was a "disease of civilization" and did not affect primitive races. When Austen Chamberlain was colonial secretary in Britain he became interested in this problem and arranged for pathologic specimens from all over the Empire to be made available for study. The result of this was to show that all races investigated were found to be subject to cancer but that the apparent incidence was influenced by the expectation of life of the various cultural groups. In other words, not every group lived to the "cancer age," but this was a matter determined by quite other factors than proneness to cancer, which was found to be similar for all groups studied.

In the realm of ophthalmology environmental factors may play a much greater part. In certain diseases of old age, for example, cataract and senile macular degeneration, it is obvious that expectation of life plays a large part in determining incidence. In other diseases, however, for example, sympathetic ophthalmitis following perforating injury, it will have no influence, type and frequency of injury and general environmental conditions being of more importance.

Diet may, indeed must, have a large influence and there still exist groups of people living and having lived for centuries on curious and, to us, very restricted diets. Does anyone know the effect on, for example, cataract, glaucoma, myopia, or nutritional eye disease, of living on a diet of tsampa (barley

meal), yak butter, and tea as do the Tibetans, or of plantains (the Baganda) or milk and blood (the Masai), or reindeer meat (the Lapps), or seal meat (the Eskimos) or kangaroo and lizard (the aboriginal Australian), or root vegetables and pork (the New Guinea highlanders)?

It is encouraging that already something is known of some of these people—studies on the Baganda and the Masai exist. Eskimos do not suffer from trachoma but phlyctenulosis is common, while this has died out in London and is seldom seen in Australia. The distribution of trachoma is fairly well-known, though its incidence in Thibet, Greenland, Dutch New Guinea, Patagonia, and so on, does not seem to be recorded.

We are only just waking up to the surprising behavior of viruses which affect the eye. Why are they more common than bacterial infections in the Mongolian races? How have the epidemics of epidemic keratoconjunctivites and APC viruses moved about the world and what has determined their appearance? One could multiply these questions of infection ad infinitum and with the present widespread facilities for travel they are assuming more importance.

Again, glaucoma is known to affect Negroes in the United States and it is sometimes said that a deeply pigmented iris may predispose. Why therefore is it relatively rare among Australian aboriginals and New Guinea highlanders? Is its incidence known in Negroes still living a tribal life in Africa? Is this the same as for American Negroes? And so on. . . .

The questions are endless, but soon the raw material, the untouched traditional life, will have gone and the natural history of eye disease can never be recaptured.

Workers on specific eye diseases have already given us much. Trachoma, onchocerciasis, ocular leprosy, and cataract have all been studied in the areas most involved but not very many surveys of the total ocular condition of races, tribes, and regions have been undertaken. Some of the earlier anthropologists investigated color vision in native races[1] but were unable to diagnose disease. Some physicians investigating other diseases have added to the uncertainty by anomalies such as the confusion of ocular leprosy with trachoma where both are rife. No one has conducted any extensive research into problems of refraction, muscle balance, and binocular vision in races other than of European stock. One could multiply the examples endlessly and needlessly.

It is as well, therefore, to get down to a few specific instances of surveys to demonstrate the kind of suggestive facts which may be discovered from them. In order to assess the geographic distribution of eye disease it is necessary to undertake widespread surveys which include a study of climate, diet, habits, insect pests, and any other factors, including possible racial immunity. Such surveys have recently been sponsored by the Western Australian Public Health Department and by the Commonwealth Department of Territories. Much that is suggestive has come out of them but much remains to be done.

Four surveys[2] were initially planned and carried out, namely, the South-West, the Eastern Goldfields, and the Kimberley District of Western Australia, with fourth, the territories of Papua and New Guinea.

We will deal first with the results of these four surveys which form a unified investigation of a large continuous area of the earth's surface. Subsequent work has been done, and is still in progress, on adjacent regions and on specific problems, such as the distribution of pathogenic bacteria. These will be dealt with later.

First four surveys

The area studied in the first four surveys comprises a tract of continent and islands stretching from 35 degrees south to the equator and involving the examination of more than 23,000 individuals. It includes almost every possible climate (save arctic conditions), temperatures from freezing to

120°F., altitudes from sea level to 12,000 feet, rainfalls from five to 200 inches, and sea coast, desert, agricultural, and mountain areas.

The ways of the people vary also, from settled agriculturists on a mixed diet, villagers on an almost vegetarian diet, nomads on an almost pure protein diet, and fish eaters of the coast. Some of the people are warlike, some peaceful. Some are deeply pigmented, others white. Many races are concerned, white settlers, European migrants, Australian aboriginals, Chinese, Malays, Melanesians, and Highland tribesmen in New Guinea.

Trachoma

In all the surveys, which are of diseases of the anterior segment only, trachoma heads the list of diseases found and a study of this shows that only two factors are involved in its spread, namely, contact in unhygienic conditions, and, as an exacerbating factor, a dry dusty climate. The study of the spread by contact links very interestingly in New Guinea with the history of the islands. This theme would take too much time to expand here. It has been dealt with in the government report on the survey and shows that trachoma is not indigenous but was, and still is, being imported from outside the islands. Other diseases fall far behind trachoma. I would like to mention a few peculiarities which have been brought to light in the various regions.

Pterygium and cataract

From the equator south to Perth the next commonest pathologic condition is pterygium, but in the southwest of Western Australia it is marginal blepharitis. There appears to be a strong racial susceptibility to this latter in persons of pure European descent. It did not occur at all in Papua, New Guinea, or New Britain (over 13,000 native persons examined), and was rare among Australians, being only found in white persons and a few half and quarter castes, and quite unknown in full-blood aboriginals.

Senile cataract was found in 136 persons (out of 13,268 examined) in New Guinea, in 65 of 2,866 persons in the Kimberleys, in 22 of 2,203 in the Eastern Goldfields, and in 19 of 5,578 in the southwest of Western Australia. In places north of Perth to the Australian coast at Wyndham the type was almost always a nuclear sclerosis, irrespective of race, while in New Guinea and in the southwest more of the soft water-cleft type of cataract was found. A correlation seems possible with atmospheric humidity though not with temperature.

Glaucoma

Glaucoma was rare in all the surveys, though only cases with impairment of sight were noted since few fundi were examined. In the 13,268 persons examined in Papua and New Guinea, it occurred once only and that in Port Moresby. No sign of it was found among the tribesmen. In the Kimberleys eight cases (of 2,866 persons examined) were found. In the Eastern Goldfields, and the desert, one case in a white man was found (of 2,203 persons examined) and in the south-west one case (white) in 5,578 persons. Among the white population of Perth it is relatively common, forming, in one private practice, five percent of the patients seen. It is very rare in native races. Can there be a correlation with salt and fluid intake, and with sodium-potassium balance? There would seem to be a field for biochemical work here.

Leprosy

Uveitis also appeared rare in both native and white persons. In New Guinea 22 cases were found (in 13,268 persons). Of these, two were kerato-iritis of leprosy. This disease occurs in the South Pacific islands and in the Kimberley district of Australia and occasionally in the north-west.[3] One must have it constantly in mind since, although it

is not common, many cases go undetected for years.

In the Kimberleys 51 cases of ocular leprosy (various types, only 21 with uveitis) were found and one case of iritis of unknown cause. The large number of cases of leprosy is accounted for by the inclusion of the leper colony at Derby in the survey. Of these 51 cases, 47 were in this leprosarium, which housed 273 persons.[3] Uveitis from other causes was not found in the Kimberleys. In the Eastern Goldfields no case was found in 2,203 persons and one case only of iritis in the southwest in 5,578. In this last survey, however, the majority of persons examined were in the younger age groups.

Uveitis, other than that due to Hansen's disease, would appear to be rare in this portion of the world and one also gains this impression in private practice, as compared with England. While considering the findings in a leprosarium, I must digress to point out that active trachoma is not found among these patients, since the sulfones used in their treatment are completely effective against it.

The relative rarity of nonleprous uveitis suggests the possibility of a correlation with tuberculosis, which is more common in the territories than in the Kimberley aboriginals. Much more work is required on this, however, before any conclusion can be arrived at. No work whatever has been done on the presence, or absence, of toxoplasmosis, though it is known to occur in Perth.

Strabismus

Another interesting feature of these surveys is the apparent racial difference in the occurrence and type of strabismus. In Papua and New Guinea natives 20 cases were found in 13,268 examinations (0.15 percent). Five were divergent and 15 convergent. There can be little implication here of correlation with early close work at school. It was not possible to delve into the family histories or refractions, so little can be said as to cause. In the Kimberleys, on the other hand, five cases of divergent squint were found in full bloods (0.3 percent), and among colored persons six cases of squint (one percent). One case was divergent and five convergent. On the other hand among white persons the incidence was 3.2 percent but five of the 22 cases found were secondary to injury or congenital anomaly. Six of the remainder were convergent.

In the Eastern Goldfields and the southwest together no case of either convergence or divergence was found in 798 full bloods examined.

Taking the colored and white persons examined on these surveys together we find among 6,983 persons (4,776 white, 2,207 caste) 103 cases of strabismus, practically all in white persons and practically all convergent. The percentage of convergent squint is high in private practice in Perth and in many cases genetic inquiry reveals its hereditary nature. These findings are suggestive that more work should be done on the racial occurrence of binocular imbalance. Why did no one of approximately 2,500 full blood Australian aboriginals show concomitant convergent strabismus?

Nutrition

We were also concerned, especially in view of present controversies on the state of nutrition of aboriginal Australians with ocular signs of avitaminosis. In Papua and New Guinea there are certainly seasons of protein deficiency, although the Australian aboriginal's diet is a high protein one on a "feast and famine" basis, in the few remaining purely tribal groups. We found no correlation with diet of any eye disease, other than possibly glaucoma and cataract, which obviously require much more work.

In Papua and New Guinea, three cases of nutritional deficiency were found (B-complex deficiency) affecting the eyes. In the Australian surveys no cases of ocular avitaminosis were found among full bloods or caste natives, though a few cases of mild

scurvy were noted in children on ill-balanced school diets. A few cases of B-complex deficiency have been seen in private practice in white Australians.

In certain areas of the north, however, a profound anemia may occur, the everted lids appearing paper white. The causes are multiple, ranging from hookworm and other tropical conditions, to ritual venesection, which is a part of some tribal ceremonies. This latter is a nice example of regional pathology of cultural causation.

Conjunctival infections

A word must be said concerning conjunctival infections other than trachoma. These fall into two main groups, namely acute and subacute bacterial infections, mostly due to the Koch-Weeks bacillus and the Staphylococcus aureus, and the group of nontrachomatous follicular reactions. The epidemics of mucopurulent conjunctivitis are associated with the hot, dry, dusty regions and affect white school children rather more than natives. They may be a factor in the spread of trachoma but there is no direct evidence of this in these surveys. The epidemics occur once or twice a year and efforts are now being made to cut them short by more efficient treatment and prophylaxis.

Of the nontrachomatous folliculoses we know very little so far. The common "follicular conjunctivitis" associated often with enlarged tonsils and adenoids occurs almost exclusively among white children. In the surveys, 215 cases were seen in territories of Papua and New Guinea, at least 10 percent of them in white children. In Australia 236 cases were noted, practically without exception in white children. Of the other follicular virus diseases in Australia we know little. There does not appear to be any inclusion blenorrhea. Epidemic keratoconjunctivitis was well known in the past but is rare now. Newcastle disease has been reported in the eastern states and recently pharyngoconjunctival fever has appeared in Western Australia. Five cases in Perth have been seen but none was found in the routine surveys. Much more study of the adenoviruses is required here.

Injuries

In any study of the relation of the environment to the incidence of disease we must include the nature of the more common injuries and their results. In an industrialized community, metallic perforating injuries will be common, in a tribalized society, arrows and spears will be the agents of perforation, and so on.

In New Guinea the people are jungle dwellers forever on the warpath, racked by intertribal feuds, only now with difficulty being controlled by the government. In the survey of territories of Papua and New Guinea we saw 378 cases of scarring (perforating and nonperforating) from injuries (sharp grasses and thorns, arrows, spears, stones, clubs, and so forth); 304 of these eyes were blind. Practically no case had had any treatment, yet no case of sympathetic ophthalmitis was found.

In the Kimberleys, 114 cases of corneal scarring (both perforating and nonperforating) were seen. Injuries here were from sticks and spears, arrows not being known to the Australian native. Again no treatment had been given and no case of sympathetic ophthalmitis was seen.

The same applies to the Goldfields and the southwest though here we have a more civilized community conditioned to seek medical aid. Twenty-three perforating injuries, all cleanly healed, were seen. This apparent absence of sympathetic inflammation is extraordinary and merits attention. If it means anything, it would appear to be against the theory of pigment allergy and in favor of an infective agent, whose distribution may not be world-wide.

Congenital anomalies

Another subject which has naturally interested me is the occurrence of congenital anomalies in primitive races. As is to be

expected the grosser abnormalities are eliminated by the individual struggle for existence and by natural selection. More drastic methods were also in use among the tribal Australians before the various missions provided a refuge for the unfit. In the New Guinea territories life is of a less harsh tempo than in the Australian bush and certain anomalies are understood and tolerated, for example, albinism. This occurs in the Trobriand Islands and elsewhere in the territories. I saw seven cases in native islanders but none in Australian aboriginals though there were eight among white Australians.

As Table 1 shows, the territories of Papua and New Guinea natives have the highest percentage and the greatest variety of anomalies. The Kimberleys stands next in the list, followed by the southwest, mainly a white population, and the Goldfields, largely aboriginals still tribal.

Many of the anomalies are of quite a minor character and have no meaning from the point of view of survival. The commonest one everywhere among pigmented races is the nonmalignant conjunctival melanoma, which is apt to frighten the oculist used only to European patients. However, no one here has ever seen one become malignant and I have watched several and they do not change.

No case of retrolental fibroplasia nor of the rubella syndrome was seen. New cases of the rubella syndrome are now rare and the victims of the original epidemic, which enabled Sir Norman Gregg to make the discov-

TABLE 1

OCCURRENCE OF CONGENITAL ANOMALIES

Anomaly	Tapua and New Guinea	Kimberley	Southwest	Goldfields	Total
Nonmalignant melanoma conjunctivae	70	13	3	2	88
Microphthalmia	12	3	3	—	18
Albinism	7	—	8	—	15
Congenital cataract	11	—	—	—	11
Angioma conjunctivae	—	1	8	1	10
Buphthalmia	3	2	—	1	6
Grape-seed bodies	5	—	—	—	5
Persistent pupillary membrane	4	—	—	—	4
Retinitis pigmentosa	3	—	—	—	3
Conical cornea	2	1	—	—	3
Microcornea	2	—	1	—	3
Corectopia	2	—	—	1 (with coloboma)	3
Epiblepharon	1	—	2	—	3
Melanosis iridis		1	1	1	3
Ocular torticollis	—	—	3	—	3
Ptosis and epicanthus	—	—	2	—	2
Nevus of lid	—	2	—	—	2
Dermoid of conjunctiva	1	—	1	—	2
Atypical coloboma	1	—	—	—	1
Epicanthus	1	—	—	—	1
Ptosis	1	—	—	—	1
Absence external rectus	—	1	—	—	1
Aniridia	—	1	—	—	1
Dislocated lenses	—	1	—	—	1
Nystagmus	—	1	—	—	1
Posterior lenticonus	—	1	—	—	1
Melanoma of lid	—	—	—	1	1
TOTAL	126	28	32	7	193
Persons examined	13,268	2,866	5,578	2,203	23,915
Percentage	0.9	0.9	0.5	0.3	0.8

ery, are now practically all in Perth and were not included in the survey. Retrolental fibroplasia is very rare in Western Australia since the country hospitals were not equipped with modern oxygen apparatus at the time of Reese's and Ashton's work.

Tables 2 through 5, which show the incidence of disease in the areas covered by the four surveys sponsored by the Western Australian state and the federal government, are taken from the published government reports which should be consulted for a detailed explanation of their meaning. It is to be noted that these are surveys of the population at large and are not comparable with

TABLE 2

INCIDENCE OF DISEASE OF THE ANTERIOR SEGMENT OF THE EYE IN SOUTH-WEST OF WESTERN AUSTRALIA

Disease	No. of Cases	Percentage of All Disease
Trachoma	1,308	63.62
Marginal blepharitis & stye	179	8.71
Follicular conjunctivitis	124	6.03
Strabismus	85	4.13
Conjunctivitis	81	3.94
Pterygium	68	3.31
Purulent ophthalmia	27	1.31
Meibomian cyst & abscess	27	1.31
Concretions	19	0.92
Cataract	19	0.92
Perforating injury	17	0.83
Hem- & lymphangioma of conjunctiva	8	0.39
Albinism and nystagmus	8	0.39
Subtarsal foreign body	7	0.34
Phlyctens	6	0.29
Keratitis & conjunctivitis (measles)	5	0.24
Eye excised (abscess & injury)	4	0.19
Lacrimal obstruction	4	0.19
Injury to conjunctiva	4	0.19
Melanoma of conjunctiva	3	0.15
Ocular torticollis	3	0.15
Eczema of lids	3	0.15
Nonperforating injury	3	0.15
Microphthalmia & congenital unilateral high myopia	3	0.15
Lid injury	3	0.15
Senile ectropion	3	0.15
Corneal abrasions & scars	2	0.09
Pediculosis of eyelashes	2	0.09
Glaucoma simplex	2	0.09
Ptosis-epicanthus	2	0.09
Lid papilloma	2	0.09
Optic atrophy (meningitis)	2	0.09
Facial palsy	2	0.09
Epiblepharon	2	0.09
Alopecia of eyebrows	2	0.09
Mustard gas keratitis	2	0.09
Sebaceous cyst of lid	1	0.05
Unequal pupils	1	0.05
Melanoma iridis	1	0.05
Epithelioma of lid	1	0.05
Detachment	1	0.05
Iritis	1	0.05
Iridodialysis	1	0.05
Cyst of gland of Moll	1	0.05
Psoriasis of lids	1	0.05
Spastic entropion	1	0.05
Phthisis bulbi	1	0.05
Microcornea	1	0.05
Dermolipoma of conjunctiva	1	0.05
Spring catarrh	1	0.05
Xanthelasma	1	0.05
TOTAL	2,056	99.95

TABLE 3

INCIDENCE OF DISEASE IN EASTERN GOLDFIELDS SURVEY OF WESTERN AUSTRALIA
(2,203 persons examined; 1,062 cases found)

Disease	No. of Cases	Percentage of All Diseases
Trachoma	729	68.64
Pterygium	52	4.90
Marginal blepharitis	50	4.71
Error of refraction other than myopia	36	3.39
Conjunctivitis	32	3.01
Follicular conjunctivitis	29	2.73
Nuclear sclerosis (cataract)	22	2.07
Strabismus	18	1.69
Concretions	16	1.51
Myopia	14	1.32
Corneal scars	12	1.13
Meibomian cyst	6	0.56
Adherent leukoma	6	0.56
?Congenital syphilis	5	0.47
Traumatic cataract	4	0.38
Unequal pupils	3	0.28
Purulent ophthalmia	3	0.28
Lid papilloma	3	0.28
Lid injury	3	0.28
Hyperthyroidism	2	0.19
Melanoma of conjunctiva	2	0.19
Melanoma of iris	1	0.09
Congenital choroiditis	1	0.09
Blocked tear duct	1	0.09
Melanoma of lid	1	0.09
Spastic entropion	1	0.09
Cicatricial ectropion	1	0.09
Senile ectropion	1	0.09
Essential shrinkage of conjunctiva	1	0.09
Buphthalmia	1	0.09
Senile macular degeneration	1	0.09
Embolus of central artery	1	0.09
Sebaceous cyst of lid	1	0.09
Optic atrophy and hydrocephalus	1	0.09
Coloboma and corectopia	1	0.09
Chronic glaucoma	1	0.09
TOTAL	1,062	99.54

TABLE 4

INCIDENCE OF DISEASE IN THE KIMBERLEY DISTRICT OF WESTERN AUSTRALIA
(2,866 persons examined; 1947 cases found)

Disease	No. of Cases	Percentage of All Diseases
Trachoma	1,199	61.58
Pterygia	118	6.06
Corneal scars	114	5.86
Conjunctivitis	90	4.62
Follicular conjunctivitis	83	4.26
Cataract	65	3.34
Ocular leprosy	51	2.62
Concretions	44	2.26
"Purulent ophthalmia"	28	1.44
Strabismus	27	1.39
Marginal blepharitis	23	1.18
"Bung eye"	15	0.77
Conjunctival melanoma	13	0.67
Meibomian cyst	9	0.46
Glaucoma	8	0.41
Phlyctens	8	0.41
Subconjunctival hemorrhage	8	0.41
Lid papilloma	4	0.21
Lymphangiectasis	3	0.15
Microphthalmia	3	0.15
Unequal pupils	3	0.15
Angioma	2	0.10
Buphthalmia	2	0.10
Interstitial keratitis	2	0.10
Pinguecula (large)	2	0.10
Nevus of lid	2	0.10
Traumatic cataract	2	0.10
Absence of external rectus	1	0.05
Aniridia	1	0.05
Blepharospasm	1	0.05
Conical cornea	1	0.05
Dislocated lenses	1	0.05
Epithelial dystrophy	1	0.05
Flash burn	1	0.05
Foreign body (sclera)	1	0.05
Iritis	1	0.05
Lid abscess	1	0.05
Lid injury	1	0.05
Melanosis iridis	1	0.05
Mucocoele	1	0.05
Nystagmus	1	0.05
Posterior lenticonus	1	0.05
Rodent of lid	1	0.05
Spastic entropion	1	0.05
Traumatic midriasis	1	0.05
Severe headache	1	0.05
TOTAL	1,947	99.95

analyses of attendances at hospital clinics. In a survey the person does not attend because he has an ocular complaint but because he is requested to appear. He may, or may not know that he has anything wrong. In a clinic or out-patient department every person attends with a complaint. (The four surveys can be obtained on application to the Public Health Department, Perth, Western Australia.)

NUTRITIONAL EYE DISEASE

The questions of nutritional eye disease and of the distribution of bacteria next engaged our attention and additional expeditions were planned with these subjects in mind.

It is known that in Southern India, in parts of Africa, and in Europe at times (for example, in Denmark during the First World War), vitamin-A deficiency has been a serious cause of blindness. During the Second World War the importance of tropical nutritional amblyopia was realized from the number of cases which occurred in prisoner-of-war camps.[4] This condition, the exact cause of which is still obscure, is also known to exist in the West Indies and in the Middle East. Malnutritional keratoconjunctivitis,[6] also a complex and little understood cause of blindness, has been described among the Bantu and, during the last 25 years, many advances in our understanding of the ocular effects of thiamine and riboflavin deficiency have been made.[7]

Since our first surveys did not reveal any outstanding signs of nutritional eye disease and since reports of starvation among the Australian aboriginals in the Central Desert areas were being received, an expedition was sent to the Rawlinson ranges which extend along the borders between South Australia, Western Australia, and the Northern Territory. The inhabitants of this area are few and live in nomadic hunting groups, constantly following the game. They live on a "feast and famine" basis, often enduring great hardship, travelling long distances without food or water and then, when a kill is made, gorging themselves on partially cooked meat. Every part of the animal is eaten. They also pick berries, wild fruits, and leaves and dig for wild yams and lily roots.

Their appearance is often thought to be characteristic of malnutrition since they are

TABLE 5

INCIDENCE OF DISEASE IN THE TERRITORIES OF PAPUA AND NEW GUINEA
(13,717 persons examined; 8,987 cases found)

Disease	No. of Cases	Percentage of All Diseases
Trachoma	7,165	79.73
Pterygium	381	4.25
Corneal scars inc. perforating & nonperforating ulcers & injuries	378	4.22
Follicular reaction other than trachoma	225	2.51
Senile cataract inc. operated cases	136	1.52
Concretions not associated with trachoma	107	1.19
Conjunctivitis other than trachoma and follicular reaction	95	1.06
Arcus senilis	84	0.93
Conjunctival melanoma	70	0.78
Developmental anomalies	58	0.65
Lid margin infections (hordeolum, meibomian cyst, marginal bleph.)	46	0.51
Traumatic cataract	25	0.28
Lid injuries & subtarsal for. bodies	24	0.27
Old uveitis inc. secondary glaucoma	20	0.22
Conjunctival scars not due to trachoma	19	0.21
Dislocated traumatic cataract	19	0.21
Dislocated senile cataract	16	0.18
Entropion & ectropion not associated with trachoma	15	0.17
Convergent strabismus	15	0.17
Ophthalmia neonatroum	13	0.14
Phlyctenular scars	11	0.12
Deep keratitis	10	0.11
Keratitis	7	0.08
Iridodialysis	7	0.08
Optic atrophy	7	0.08
Divergent strabismus	6	0.07
Ruptured iris sphincter	4	0.04
Nutritional deficiency	3	0.03
Subconjunctival hemorrhage	2	0.02
Lymphangiectasis	2	0.02
Ocular leprosy	2	0.02
Chorioretinal degeneration	2	0.02
Dacryocystitis apart from trachoma	2	0.02
Cranial nerve palsy	2	0.02
Complicated cataract	2	0.02
Nits on lashes	2	0.02
Albuminuric retinitis	1	0.01
Orbital injury	1	0.01
Perivasculitis retinae	1	0.01
Tobacco amblyopia	1	0.01
Glaucoma simplex	1	0.01
TOTAL	8,987	100.00

thin with protuberant bellies. The exact cause for this is at present unknown but there is evidence that the diet is unsuitable during the weaning period and cases of deficiency (scurvy and kwashiorkor) may occur then until adjustment is achieved. I therefore was prepared to find some nutritional eye disease and careful examination was made for Bitôt's spots, keratomalacia, and xerophthalmia (vitamin-A deficiency), for diminished visual acuity, nystagmus, cracked canthi, and central color scotoma (vitamin-B_1 deficiency), for circumcorneal vascularization, photophobia, and lacrimation (vitamin-B_2 deficiency), for ocular signs of scurvy, and for phlyctenular disease.

In all, 438 aboriginals were examined. Of these 337 had trachoma but not one showed any ocular signs of malnutrition, though five had scurvy and one kwashiorkor.[8] The general medical findings of the other members of the expedition did not reveal much evidence of malnutrition according to ordinary standards.[9]

A possible explanation of the absence of detectable signs in a particularly unde-

veloped community is that the periods of stress involve actual starvation rather than exposure to a continued unbalanced diet, as is the case, for instance, in asiatic countries. Much more work should be done on these people as their food habits over an entire year are not known, nor are the vitamin contents of all the native foods.

Very little disease other than trachoma was found. Visual acuity was good, being above 6/6 in 119 of 145 persons tested and from 12/5 to 17/5 in 23 of these. The tests were done in daylight with the illiterate E test so that the results would be expected to be somewhat better than by standard illumination. Certain conditions common in white Australians were absent, for example, styes and marginal blepharitis, myopia, convergent squint, glaucoma, soft cataract, color blindness, and mucopurulent conjunctivitis.

Distribution of bacteria

The absence of signs of bacterial infection in the natives who live most unhygienic lives in a very remote place where they see few Europeans is of interest. Throughout the state generally full-blood aboriginals appear to suffer very little from staphylococcal infections until they become assimilated to the white Australian way of life. It was therefore decided to investigate the bacterial flora of the eyes of a group of natives even farther removed from civilization than the Rawlinson Ranges tribe. With this object Dr. MacLean of the Commonwealth Serum Laboratories, Dr. John Crotty, pathologist to the Northern Territories Public Health Department, and I went to Arnhem Land with the laboratory equipment necessary to take conjunctival smears and cultures from anything up to 100 natives.

We visited Groote Eylandt first. This is an island about 35 miles across lying on the western side of the Gulf of Carpentaria. The population is only a few hundred persons. There is a small mission station but little contact with Europeans. We next went to Goulbourn Island, which lies off the north coast of Arnhem Land, to Oenpelli on the mainland, and finally to a native settlement just outside Darwin where there was more European contact.

In all, we examined and cultured 66 persons, mostly children and adolescents. Most of them had active trachoma but in none did there appear clinically to be gross secondary infection. Many had, however, a severe mucopurulent nasal discharge and in 55 a nasal swab was done as well.

The results were surprising in that practically no pathogens were found. Many cultures of the conjunctiva were sterile though most grew S. albus. Sometimes coliforms were present, and sometimes nonhemolytic streptococci. Gram-negative cocci occurred also. One culture alone grew S. aureus and two nasal cultures yielded a Beta hemolytic streptococcus. There were two cultures of hemolytic staphylococci and two of Friedlander's bacillus. The results were, pathologically speaking, of no importance and serve to emphasize what is already obvious clinically, namely, the extreme rarity of pathogenic or pyogenic bacteria. These results, which will be published in detail shortly, explain the mildness of the trachoma which is practically self-limiting and free from complications in these areas.

Comment

Enough has been said to show that findings of great interest can be obtained by studying isolated racial and cultural groups where such still exist. One could expand this subject of geographic distribution of disease almost indefinitely. It would seem to offer a great field for future work. Certain pointers indicated by the work to date could be followed or the method could be extended to include fundus conditions and refraction. One line, that of color blindness in relation to race, has already been followed and the results published last year.[10] Work on vascular disease of the fundus and senile macular degeneration would almost certainly produce interesting results. It is to be hoped

that in the future, time and personnel will be found to investigate these questions before all distinctions of diet, custom, and occupation are lost in these still relatively untouched areas which western civilization seems determined to "open up."

Summary

1. An account is given of the occurrence of diseases of the anterior segment of the eye in four areas of Australasia—the territories of Papua and New Guinea, the Kimberleys, the southwest of Western Australia, and the Eastern Goldfields.

2. The following diseases are specially considered: glaucoma, cataract, strabismus, pterygium, trachoma, uveitis, sympathetic ophthalmitis, leprosy, nontrachomatous folliculosis, nutritional disease, and congenital abnormalities.

3. Possible meanings and lines for future investigation are indicated.

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THE YELLOW PIGMENT OF HUMAN LENSES*

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Introduction

The normal human lens develops a visibly yellow coloration with age. Little is known concerning the nature of the pigment responsible for this color. There is a strong discoloration of the lens in cataracta brunescens (cataracta nigra) described by Cordes.[1] The work done on this pigment has been summarized by Duke-Elder[2] who states that it may be melanin, lipofuscin, or "one of the related but little understood substances" and that this "same substance in smaller concentration may to some extent at any rate be responsible for the yellow color of the senile lens."

Work was undertaken in this laboratory to identify more closely the yellow pigment of lenses.

Material and Methods

Lenses were obtained either from eye-bank material or from surgery. Two groups were collected.

1. Twenty yellowish cataractous lenses and one brunescent cataract were obtained after surgery through the courtesy of Dr.

* From the Francis I. Proctor Foundation for Research in Ophthalmology, University of California Medical Center.

F. C. Cordes and staff. These were accumulated in 1N. NaOH.

2. Approximately a similar number of yellowish lenses were collected in alcohol from eye-bank eyes.

The absorption spectra were obtained either with a Beckman DU spectrophotometer or a Cary ultraviolet recording spectrophotometer.*

Urochrome was isolated from urine by slight modifications of the methods of Garrod and Hohlweg as reported by Fox.[3]

Melanin was isolated and purified from black horsehair by the method of Schmidli and Robert.[4]

Results

The character of the absorption spectra of whole single lenses was first determined by dissolving them almost completely in thioglycolic acid. The resultant opalescent solution was clarified by centrifugation. The character of the absorption spectra of these solutions, obtained either from a yellow lens or a colorless lens or the difference spectra between a colored lens versus a colorless lens, were all similar, with increasing extinction from the blue end of the visible spectrum into the ultraviolet region and with no distinct peak. This preliminary work indicated that the yellow pigment is present in colorless lenses but in too low a concentration to be apparent visually. It also showed that the pigment was probably among the compounds referred to earlier.[2]

On the assumption that the yellow material had properties similar to melanin, the first group of yellow cataractous lenses were treated according to the methods for isolating melanin.[4] It was soon apparent that the pigment was not melanin as it was both acid and alcohol soluble. The pigment was then purified by precipitation from alcohol by ether or carbon tetrachloride. The major isolation procedures carried out on the second group of lenses were homogenization in a buffer at pH = 7.0, treatment with trypsin, centrifugation and dialysis of the supernatant to separate the pigment from the protein. The material isolated from both groups reacted the same to all tests and no further distinction is made between the pigments obtained from either the cataractous or the normal group.

To confirm that the pigment was not melanin it was subjected to treatment with alkaline $KMnO_4$ with subsequent addition of oxalic acid. The melanin control was bleached by the permanganate but the yellow lens material had a slightly higher optical density. This intensification of color is characteristic of urochrome.[3]

There are a number of naturally occurring yellow animal biochromes which may be identifiable with the yellow lens pigment. These include principally urochome, urobilin, stercobilin, lipofuscins, thiochrome, and riboflavins.

Urochrome is apparently a decomposition product of protein and is the principal pigment of normal urine. Urobilin in urine is the same as stercobilin in feces and they may be distinguished from urochrome by an absorption peak at 494 mμ[5] and by the Gmelin test[6] which is positive for most linear tetrapyrrole compounds. The vague class of compounds known as lipofuscins or chromolipoids are oxidative derivatives of fat. They are easily distinguished from urochrome by their solubility in fat solvents. Both thiochrome, the yellow oxidation product of thiamine, and the riboflavins have strong absorption peaks.

The yellow pigment of the lens and urochrome are soluble in dilute acids and bases and alcohol and insoluble in ether and chloroform. They both yield negative Gmelin tests. They give similar absorption spectra from 300 to 700 mμ but the spectra have no characteristic maxima or minima. When applied to filter paper they show blue fluorescent spots. It is not known if this material is the

* Spectra obtained with this instrument through the courtesy of Louis A. Strait, Spectrographic Laboratory, School of Pharmacy, University of California School of Medicine.

same fluorescent material of the lens as measured by Brolin and Cederlund.[7]

Discussion

The various chemical and physical tests made on the lens pigment indicate that it is related to urochrome rather than to several other naturally occurring animal biochromes which have been postulated to this time.

Because urochrome[8] is as yet so ill-defined chemically, it is difficult to identify unambiguously the yellow pigment of the lens as urochrome.

The evidence indicates that this same pigment occurs in both normal and cataractous lenses. Since only one brunescent cataract was included in the cataractous group, it is not known if the pigment in this type of cataract is the same as that which was isolated. There is apparently no casual relationship between the pigment and cataracts.

It might be difficult to explain the presence of melanin or pyrrole compounds derived from blood because of the nonpigmented, avascular nature of the lens. Since urochrome is probably derived from nonspecific protein material, its presence in the lens may be accepted on a physiologic basis.

Summary

1. The yellow pigment isolated from normal and cataractous lenses appears to have similar physical and chemical properties to urochrome isolated from urine.

2. This pigment is probably a nonspecific degradation product of proteins and apparently increases in concentration with age, finally becoming clearly visible in the older age group.

3. Its presence in both normal and cataractous lenses indicates only a casual relationship.

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THE CLINICAL ESTIMATION OF THE OCULAR RIGIDITY*

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The two methods devised for the clinical estimation of ocular rigidity (K) have in common the utilization of the principle of comparing two tonometric measurements of the intraocular pressure of which one is only very slightly, and the other one very markedly affected by the prevailing ocular rigidity. The rapidly growing popularity of Goldmann's applanation tonometer[1] will undoubtedly produce large series of rigidity estimates based on comparisons of applanation and indentation measurements.

It may be appropriate at this time to attempt an evaluation of the older method of estimating ocular rigidity in which two pressure measurements obtained by indentations of greatly different depth and size are compared with each other. Very aptly called differential tonometry by Schmidt,[2] the method of paired measurements with two measurements with two different loads was first conceived and practiced by Hagedoorn[3] in connection with the problem of calibration of Schiøtz tonometers. Unaware of Hagedoorn's work, Friedenwald[4] arrived at the method of paired tonometric readings as a logical consequence of his concept of the constancy of ocular rigidity over a wide range of intraocular pressures. His views concerning the practical aspects of the method are clearly expressed in the decennial report of the Committee on Standardization of Tonometers:[5]

"Since the clinical reading error with a mechanical tonometer is of the order of ± 0.5 scale units, the error in the difference determined from a single pair of readings is of the order of ± 1.0 scale units. Consequently a single pair of tonometric readings may lead to very large errors in the estimate of K and of P_o (the intraocular pressure just before the application of the tonometer). This error can be greatly reduced if the results of six or more pairs of tonometric measurements are averaged, but that many tonometric readings cannot as a rule be made in rapid succession without producing a pronounced massage effect and a consequent upward drift of the successive tonometer scale readings. . . . A sufficient number of pairs of measurements should be made to enable a fairly stable estimate of P_o and K."

Friedenwald thus prepared the prospective user of his method for a wide spread of its results. He also pointed out a possibility of error if multiple rigidity measurements are averaged instead of the tonometric readings. This error arises from the fact that K varies in geometric progression with arithmetic steps in scale readings which causes reading errors in the plus and minus direction not to cancel each other out.

Any method of estimating the ocular rigidity by multiple or repeated (RPTR) paired tonometric readings aims at reduction of the error inherent in single tonometric measurements which Rohrschneider and Kuechle[6] determined as ± 1.0 scale unit (± three times the standard deviation of the series of measurements). There are as yet no definite expressions in the literature of the accuracy of methods for rigidity measurements necessary or desirable for clinical purposes. Most clinicians would probably consider as clinically acceptable a method capable of placing the rigidity of a given eye within the range of two adjacent classes of Friedenwald's rigidity scale. That would allow estimates of P_o within a range of 4.0 mm. Hg or less, with the only exception of cases of very high ocular rigidity. For investigative purposes, particularly for the interpretation of tonograms, an accuracy of one class of Friedenwald's scale would be highly desirable. This scale may be thought

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of as a geometric progression in which a factor varying from about 30 to 70 percent relates the midpoints of adjacent classes. In the commonly used portion of the scale the midpoints of two adjacent classes differ by about a third to one half of the value of the midpoint of the lower class. Only the midpoints of these classes are given in the currently used tables.[7] In between values may be calculated from the formula

$$K = \frac{\log P_{t10} - \log P_{t55}}{V_{c10} - V_{c5.5}}.$$

Needless to say, the proof of the capability of any paired-reading method to accomplish any desired degree of accuracy awaits calibration by the direct method of observing the rise in intraocular pressure resulting from the intracameral injection of small, accurately measured amounts of fluid into living human eyes.

Judging from the literature the method of paired tonometric reading with Schiøtz tonometers has yielded widely divergent results in the hands of different investigators. Some[8,9] have found the reading error too disturbing to arrive at any reasonable estimate of the ocular rigidity. In the hands of other observers, particularly of Lavergne, Weekers and Prijot[10], the method has apparently worked reasonably well. It is the purpose of this study to determine how the method of paired readings works out in the hands of two experienced examiners unfamiliar with the purpose of paired readings, on patients thoroughly acquainted with the procedure of tonometry.

Material and Technique

The tonometric measurements reported herein were made on adult patients selected from the population registered and observed in the Glaucoma Clinic of the Illinois Eye and Ear Infirmary or from my private office. The basis for selection was compliance with the requirements of:

1. Having or being suspected of having glaucoma of the chronic simple, angle-closure or one of the commoner secondary types,

2. Of having a central visual acuity of at least 20/200 in each eye,

3. Of being familiar with, well relaxed, and co-operative during the tonometry, and

4. A fair degree of stabilization of the ocular tension by conservative means.

Unless stated otherwise, the rigidity tests were made while the patient was under the influence of the tension-stabilizing medication. Patients recently operated on, and particularly patients who had had extensive surgery to the sclera such as cyclodiathermy, were excluded from this study.

All measurements were made by one of two examiners with one of two certified Schiøtz tonometers of American manufacture,* during the hours from 8:30 to 10:30 A.M. or 1:00 to 3:30 P.M. and prior to any eye test at the particular visit other than the determination of the central visual acuity. The following standard procedure of measurement was used:

Applications of the tonometer of from two to three seconds' duration were made and the oscillations of the pointer were carefully observed. The whole or half scale unit closest to the average position of the pointer during the application was recorded as the reading. The averaging was done visually by the examiner. The applications were made first to the right and then to the left eye, first with the lower weight and then with the higher weight, allowing enough time for re-

* Accurate construction and low friction of the tonometer are essential requirements for rigidity measurements. With the current specifications and tolerances for Schiøtz tonometers there is the possibility of systematic differences between the estimates obtained with two or more certified tonometers. On a gauge set at indentations of exactly three and eight scale units (0.15 and 0.40 mm., respectively), one Schiøtz tonometer (1) may read 2.8/8.2 while another tonometer (2) may read 3.2/7.8. Both of these pairs of readings are within the current tolerances and the instruments are certifiable, assuming, of course, that the instruments meet all other specifications. Tonometer (1) will tend to yield smaller estimates of K than tonometer (2). In offices or in clinics in which several tonometers are used routinely it would be advisable to record the number of the tonometer together with the paired reading.

cording of the reading by the examiner before the application of the heavier load. Thus the sequence was: Right 5.5, left 5.5, right 10, left 10, and so forth.

The procedure of just one pair of measurements per clinic visit was called Procedure A. Procedure B consisted of two and C of three successive sets of paired measurements made in the same "sitting." The average time required for Procedure B was 81 seconds and for Procedure C 116 seconds. The symbols a, b, c, d, e, and f denote the tonometric scale readings at the respective steps of the procedures. The readings a, c, and e were obtained with the lighter load, b, d, and f with the heavier load. Procedure A yielded only a and b values for each eye, Procedure B, a, b, c, and d values, and Procedure C, a, b, c, d, e, and f values for each eye. The 5.5- and 10-gm. weights were used routinely; in eyes which with the 5.5-gm. weight gave readings less than two scale units the paired readings were taken with the 7.5- and the 15-gm. weights. Such eyes were not included in Series A and B.

Results

The property of repeated paired tonometric readings is of the greatest interest to the clinician in its consistency or inconsistency. This property is presented in Table 1 in terms of the spread, over one, two, or three units of Friedenwald's rigidity scale, of the rigidity estimates obtained by Procedures A, B, and C in series of 76 (A), 233 (B), and 100 eyes (C), respectively. The most important fact revealed by Table 1 is that all three procedures yielded rigidity estimates which for about 90 percent of the eyes in each series fell within two adjacent classes of Friedenwald's rigidity scale. Any of the three procedures may thus be acceptable for clinical purposes.

*Procedure A.** Table 2 may serve to exemplify the results obtainable with Procedure A. This table represents the very beginning of this study; it gives the measurements on the first 13 clinic cases who after one or two trials by the principal examiner were selected for further tests. The results were remarkably consistent and their spread decidedly smaller than what one would have expected from a method encumbered with a measuring error of ±1.0 scale units. The cause of that greater-than-expected consistency was probably the visual averaging which was an essential feature of the method.

TABLE 1*

ESTIMATION OF OCULAR RIGIDITY BY REPEATED PAIRED TONOMETRIC READINGS
RESULTS OF THREE PROCEDURES

Procedure	Spread of Rigidity Estimates in Units (classes) of Friedenwald's Scale		
	One	Two	Three
A	47	23	6
B	114	96	23
C	31	59	10

* Frequencies expressed in numbers of eyes.

The impression one gains from Table 2 is that ocular rigidity is a fairly constant property of glaucomatous, tension-stabilized eyes. The few measurements that were out of line were probably due to errors of measurement and not due to variations in ocular rigidity. This impression was supported by the fact that most of the values for P_o corresponding to the markedly deviating rigidity estimates were also out of line. This state of being out of line was quite noticeable because, as the result of the medication, P_o varied only within a narrow range in the cases shown in Table 2. In the few instances of a scale reading of two with the 5.5-gm. weight the change in the shape of the corneal indentation due to bulging of the cornea into the space between the central edge of the hole in the footplate and the edge of the plunger discovered by Moses and Hahn,[11] was just beginning to make itself noticeable in the form of slight false lowering of the ocular rigidity.

Procedures B and C. The results of Pro-

* The results of Procedure A look better than those of Procedures B and C, but only the differences between Procedures B and C, columns 1 and 2, are statistically significant, that is, very probably not due to chance.

TABLE 2

ESTIMATION OF OCULAR RIGIDITY BY MULTIPLE PAIRED READINGS
PROCEDURE A

Patient's Unit No.	Date	Right Eye			Left Eye		
		$R_{5.5}/R_{10}$	K	P_0	$R_{5.5}/R_{10}$	K	P_0
5153	5-17-56*	3.0/ 7.0	0.0353	19	3.5/ 7.5	0.0350	17
	6- 7-56	3.0/ 8.0	0.0173	26	3.5/ 8.5	0.0176	24
	9- 7-56	3.0/ 8.0	0.0173	26	3.0/ 8.0	0.0173	26
	10- 8-56	2.5/ 7.5	0.0167	29	2.0/ 7.0	0.0159	32
	10-22-56	3.0/ 8.0	0.0173	26	2.5/ 7.5	0.0167	29
	11- 5-56	3.0/ 8.0	0.0173	26	3.0/ 8.0	0.0173	26
4689	5-18-56	3.5/ 8.5	0.0176	24	4.0/ 9.0	0.0177	22
	6- 8-56	4.5/ 9.5	0.0181	21	5.5/10.5	0.0182	18
	9-28-56	6.5/11.5	0.0181	15	7.0/12.0	0.0179	14
5090	5-22-56	5.0/10.0	0.0182	19	4.5/ 9.5	0.0180	21
	6-19-56	5.0/10.0	0.0182	19	5.0/10.0	0.0182	19
	8- 7-56	4.5/ 9.5	0.0180	21	5.0/10.0	0.0182	19
5221	5-22-56	5.0/ 9.5	0.0246	16	6.0/10.5	0.0242	13
	6- 5-56	4.5/ 9.5	0.0180	21	5.5/10.0	0.0245	15
	7- 3-56	5.0/10.0	0.0182	19	6.0/11.0	0.0181	16
	8- 7-56	4.5/ 9.5	0.0180	21	5.0/10.0	0.0182	19
	9-18-56	5.0/10.0	0.0182	19	7.0/12.0	0.0179	14
5156	6- 5-56	3.5/ 8.5	0.0176	24	3.0/ 8.0	0.0173	26
	8- 9-56	4.5/ 9.5	0.0180	21	2.5/ 7.5	0.0167	29
	9-21-56	5.0/10.0	0.0182	19	3.5/ 8.5	0.0176	25
	10-26-56	3.0/ 8.0	0.0173	26	3.0/ 8.0	0.0173	26
143	8-16-56	6.0/11.0	0.0181	16	6.0/11.0	0.0181	16
	8-30-56	7.0/12.0	0.0179	14	6.0/11.0	0.0181	16
	10-23-56	7.5/12.5	0.0178	13	6.5/11.5	0.0181	15
5091	6- 7-56	4.0/ 9.0	0.0177	22	3.5/ 8.5	0.0176	24
	8- 9-56	4.0/ 9.0	0.0177	22	4.0/ 9.0	0.0177	22
	10- 9-56	6.5/11.5	0.0181	15	5.5/10.0	0.0182	19
	10-23-56	5.0/10.0	0.0182	19	5.0/10.0	0.0182	19
	10-30-56*	3.0/ 8.0	0.0173	26	2.0/ 7.0	0.0159	32
4323	8- 6-56	3.5/ 8.5	0.0176	24	3.5/ 8.5	0.0176	24
	8-20-56	4.5/10.0	0.0135	23	5.5/10.0	0.0138	20
	8-27-56	4.0/ 9.0	0.0177	22	4.0/ 9.0	0.0177	22
	9-10-56	5.0/10.0	0.0182	19	6.0/11.0	0.0181	16
	10- 4-56	5.0/10.0	0.0182	19	6.0/11.0	0.0181	16
5262	8- 6-56	5.0/10.0	0.0182	19	6.0/11.0	0.0181	16
	8-20-56	7.5/12.0	0.0233	10	8.0/13.0	0.0176	12
	8-27-56	6.5/11.5	0.0181	15	7.0/12.0	0.0179	14
	9-10-56	6.0/11.0	0.0181	16	6.0/11.0	0.0181	16
	10- 1-56	7.0/12.0	0.0179	14	7.0/12.0	0.0179	14
5061	8- 6-56*	2.0/ 7.0	0.0159	32	2.5/ 7.5	0.0167	29
	8-20-56	5.0/ 9.5	0.0246	16	5.0/ 9.5	0.0246	16
	8-27-56	5.0/10.0	0.0182	19	5.0/10.0	0.0182	19
	9-10-56	4.5/ 9.5	0.0180	21	5.0/ 9.5	0.0246	16
	9-26-56	6.0/11.0	0.0181	16	5.5/10.5	0.0182	18
5275	8- 6-56	4.5/ 9.5	0.0180	21	3.0/ 8.0	0.0173	26
	8-20-56	6.0/11.0	0.0181	16	4.0/ 9.0	0.0177	22
	8-27-56	5.5/10.5	0.0182	18	4.5/ 9.5	0.0180	21
	9-10-56	6.0/11.0	0.0181	16	4.0/ 9.0	0.0177	22
	10-22-56	3.0/ 8.0	0.0173	26	2.5/ 7.5	0.0167	29

* The asterisks denote discontinuance of the regular treatment (Pilocarpine or Carcholin) for several days prior to the rigidity measurement.

TABLE 4

TABLE 2 (*Continued*)

Patient's Unit No.	Date	Right Eye			Left Eye		
		$R_{5.5}/R_{10}$	K	P_0	$R_{5.5}/R_{10}$	K	P_0
5277	8- 7-56*	3.0/ 8.0	0.0173	26	2.5/ 7.5	0.0167	29
	8-14-56	4.5/ 9.5	0.0180	21	4.5/ 9.5	0.0180	21
	8-21-56	4.0/ 9.0	0.0177	22	4.5 /9.5	0.0180	21
	9- 6-56	4.0/ 9.0	0.0177	22	5.0/10.0	0.0182	19
	10- 4-56	5.5/10.5	0.0182	18	5.0/10.0	0.0182	19
5268	8-14-56	6.0/11.0	0.0181	16	6.0/11.0	0.0181	16
	8-21-56	9.0/14.0	0.0171	11	8.0/13.0	0.0176	12
	9- 6-56	6.5/11.5	0.0181	15	7.0/12.0	0.0179	14
	10- 4-56	6.5/12.0	0.0139	17	7.0/12.0	0.0179	14

cedures B and C are shown more fully in Table 3 where K_1, K_2, and K_3 denote the rigidity estimates based on the first (a, b), second (c and d), or third pair (e and f) of readings, respectively. All three successive paired readings yielded rigidity estimates within the same class of Friedenwald's scale (that is, $K_1 = K_2 = K_3$) in 31 out of 100 eyes. Two successive paired readings yielded rigidity estimates within the same class of Friedenwald's scale ($K_1 = K_2$ or $K_2 = K_3$) in about 50 percent of all eyes subjected to Procedures B or C. Where successive paired readings placed the rigidity estimates outside the limits of one class there was a definite trend for the second estimate to be lower than the first.

Discussion

The results of this study have a bearing on two of the many questions that have arisen with regard to ocular rigidity, namely:

1. The question of a possible superiority of one of the three procedures used here over the other two and

2. The question of further refinement of the method of repeated paired tonometric readings.

To answer these questions requires evaluation of all factors that may affect repeated paired tonometric readings. Previous investigators[5] have been aware of the massage effects of repeated paired tonometric readings, that is, the expulsion, by the application of the tonometer, of aqueous over and above the normal prevailing flow rate. There also is the possibility of a change in plasticity of the area of cornea subjected to the weight of the tonometer.[1] Minor manipulations around the eye including tonometry have also been shown or assumed to alter the intraocular pressure of one or both eyes by affecting the rate of aqueous secretion and the local and systemic vascular pressures.[12] While the massage or tonographic effect is most likely the major factor the possibility of its "contamination" with other ocular volume-changing factors unquestionably exists. The over-all magnitude of these tonometry-induced disturbances of the pretonometric steady-state

TABLE 3

Estimation of Ocular Rigidity by Repeated Paired Tonometric Readings
Results of Procedures B and C

Procedure	$K_1 = K_2$	$K_1 > K_2$	$K_1 < K_2$	$K_2 = K_3$	$K_2 > K_3$	$K_2 < K_3$
B	114	75	44	—	—	—
C	60	24	16	49	30	21

Frequencies expressed in numbers of eyes.

TABLE 4

THE DRIFT OF SUCCESSIVE PAIRED TONOMETRIC READINGS
(arithmetic means)

Procedure	a	b	c	d	e	f
B	3.91	8.44	4.05	8.67	—	—
C	3.52	7.97	3.68	8.18	3.92	8.47

can be expressed in a number of ways. One obvious way is the arithmetic means of the tonometric readings at each step of Procedures B and C. These means (table 4) show a steady upward drift, more pronounced in Procedure C than in B. It may help to visualize the magnitude of this drift to convert it into units of intraocular pressure, assuming average rigidity (0.0215). This assumption is permissible since deviations of the actual ocular rigidity from the assumed value would change mainly the absolute pressure levels but not small pressure differences which are under consideration here. The mean change in intraocular pressure during Procedure C from a point halfway between a and b to a point halfway between e and f was 1.64 mm. Hg. To the clinician it might mean more to say that during Procedure C the intraocular pressure of 83 out of 100 eyes dropped about 2.0 to 3.0 mm. Hg.

For the purpose of further analysis it is advantageous to convert the drift of the tonometric scale readings into a change in ocular volume,[13] realizing, of course, that the drift may have been only partly but not entirely due to expulsion of aqueous. In Table 5 the drift is presented as a loss of ocular fluid contents in relation to the starting points a and b to which a volume of 0 has been assigned. This method of presenting the drift brings out its time course which is apparently that of a gradual start and a slowly increasing rate of fluid loss during Procedure C. There the assumption is made that the applications of the tonometer to the individual eye were made at fairly equal time intervals. While no effort was made to observe such a regular schedule it is very likely that the measurements were made about 15 seconds apart.

The increase in the rate of fluid loss shown in Table 5 could account for the slight downward drift of the successive estimates of ocular rigidity ($K_2 < K_1$) and ($K_3 < K_2$) which is given in Table 6 for Procedures B and C. That this represented an actual change in ocular rigidity is made highly unlikely by the observations of Stepanik[14] and Ballintine[15] that there is no consistent change in ocular rigidity during tonography.

The fact that instances of $K_2 < K_1$ and $K_3 < K_2$ were more frequent than $K_1 < K_2$ and $K_2 < K_3$ (table 3) was probably also

TABLE 5

THE DRIFT OF SUCCESSIVE TONOMETRIC READINGS

Steps in Procedure C	a	b	c	d	e	f
			c–a	d–b	e–a	f–b
Drift in Scale units	0	0	+0.16	+0.21	+0.40	+0.50
Drift in cu. mm.	0	0	−0.272	−0.418	−0.680	−1.040
			d–c	e–d	f–e	
Rate of Drift in cu. mm.			0.146	0.262	0.360	

TABLE 6

OCULAR RIGIDITY ESTIMATED FROM THE MEANS OF SUCCESSIVE PAIRED TONOMETRIC READINGS

Procedure	K_1	K_2	K_3
B	0.0240	0.0226	—
C	0.0254	0.0244	0.0239

a manifestation of the slowly rising rate of fluid loss which caused the 10-gm. reading to get slightly "ahead" of the 5.5-gm. reading.

The technique used in this study was not accurate enough to permit the establishment of correlations between the drift in scale readings (or the ocular volume change) and parameters such as the initial tonometric scale reading or the rise in intraocular pressure during tonometry ($P_t - P_o$). All that can be said at present is that the drift varied somewhat in magnitude. So far it has not been possible to produce a truly representative control series. Normal eyes subjected to Procedure C show a markedly larger drift than the eyes of the patients on whom this study is based; but the average initial tonometric scale reading of the normal eyes is in the neighborhood of six scale units (with the 5.5-gm. load) which makes the two series not strictly comparable. A study of normal controls tested with a 3.0- and a 7.5-gm. weight has been under way for some time but has not progressed to the point of representativeness, particularly with regard to calibration data pertaining to the 3.0-gm. load.

Conclusions

The foregoing discussion brings out the advantages of Procedure A, that is, one pair of readings at each office or clinic visit, taken with appropriate loads and under fairly uniform conditions. It is unlikely that the initial reading with the lower weight influences the subsequent reading with the higher weight. The preparations and the time necessary for a paired reading hardly exceed those necessary for a single tonometric reading. In the majority of chronic simple glaucomas under treatment Procedure A yields estimates of K which are well within two and often within one class of Friedenwald's rigidity scale. Such an accuracy is adequate for most clinical purposes.

There can be no serious objection to the repeated paired readings since repeated single readings are necessary in most chronic simple glaucomas during the initial trial period of the various therapeutic agents. The slowness of Procedure A is no serious disadvantage since situations requiring immediate action are rarely encountered in the management of chronic simple glaucoma.

The comparison between Procedures B and C is best made on the basis of the data given in Table 3. Procedure C confirmed essentially what was learned through Procedure B, namely, a 50 to 60 percent incidence of $K_1 = K_2$ and a definite trend toward $K_1 > K_2$ in the cases where K_1 did not equal K_2. The additional measurements made in Procedure C yielded estimates for K_3 which proved to be related to K_2 in very much the same way as K_2 was related to K_1. The latter half of Procedure C, in other words, confirmed statistically the findings of the former, the earlier half. In doing so Procedure C furnished 89 instances, out of a total of 100 tests, of two of the three estimates of K being identical or well within the same class of Friedenwald's scale. Included in these 89 instances are the 31 eyes which on all three successive tests gave identical estimates for K. Interestingly enough, in half of these cases the tonometric readings remained unchanged during the entire procedure while the other half followed the pattern of the upward drift, exemplified by readings (with the 7.5 and the 15 gm. weight) such as:

4.5/10 to 5.0/10.5 to 5.5/11 or
4.0/8.0 to 4.0/8.0 to 4.5/8.5

Analysis of the 58 instances of two concordant and one discordant estimate again revealed, in a good many cases, the pattern of a slow upward drift of the scale readings in which the discordant member participated

either with its 10-gm. or with its 5.5-gm. reading only. Thereby the state of discord between paired readings was created.

In the light of this analysis it seems justifiable to consider as valid estimates of ocular rigidity not only the identical triplicates furnished by Procedure C in 31 out of 100 cases, but also the identical duplicates, and to consider the discordant third measurement as either an error of measurement or as the result of one of the paired readings being "out of step."

The analysis of these cases as well as of the cases of three discordant estimates of K can be facilitated by plots of the P_o equivalents of all six readings (a-f), again assuming average ocular rigidity. The realization that the underlying process is expressed by a descending curve of gradually increasing steepness, facilitates the recognition of the most out-of-line as well as of the most-in-line readings. From the latter it may be possible to derive an estimate of K even in cases of three discordant estimates. Ever so often, however, a set of readings may have to be discarded altogether. Needless to say, the conclusion of high ocular rigidity and correspondingly low P_o (that is, no glaucoma) should only be made on very good evidence. By the same token, the mere suggestion of low ocular rigidity (below 0.0150) calls for continued close observation of the patient.

The clinical significance of unusually high and low ocular rigidity will be dealt with in a subsequent communication.

Summary

Friedenwald's method of estimating ocular rigidity by means of repeated paired tonometric readings has been used by two experienced examiners on selected patients. The results have been consistent to a degree to make the method appear useful for clinical purposes.

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SIGNS AND SYMPTOMS OF UVEITIS*

I. Anterior uveitis

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At the time we first commenced clinical and laboratory studies on uveitis in 1947 we did not anticipate difficulty in evaluating the clinical manifestations. We were aware, however, that the development of laboratory and research techniques might take a considerable amount of time.

We soon found that it was not easy to classify the various types of uveitis. It was difficult for the three of us consistently to evaluate such lesions as keratic precipitates, iris nodules, iris precipitates, and so forth. In order that later statistical studies might be worth while we knew it would be necessary to develop some type of classification of these findings. To accomplish this we adopted the policy that each of us should examine every case, and record the observations. By this method points of difference would be revealed and eventually resolved by discussion.

It is estimated that it required about a year before we were in fairly good agreement as to the classification of signs (but not the types) of uveitis. By this time we had learned that some types of uveal inflammation tended to have a certain pattern though their etiology most often was unknown.

Classification of cases according to the concepts of Woods[1] into granulomatous and nongranulomatous forms was attempted. It soon became apparent that many failed to fall into this classification, or if they could be classified, frequently changed in character. Cases might be seen one week with the signs of a granulomatous inflammation, only to show very few features of this type of inflammation a week later. Atypical cases were common. With respect to posterior uveal inflammations we were never able to classify them into granulomatous or nongranulomatous forms with any degree of exactness.

It is hoped that our observations and classification of the findings will increase the interest of others in this problem. General agreement on classification of the findings is a basic requirement for collaborative studies. It is not possible to make a perfect classification of the various manifestations of uveitis, and we do not expect entire agreement with the one presented here. The findings are, however, based on quite detailed examinations on 1,700 cases of uveitis. This discussion may assist other groups or individuals and eventually may help shed light on the etiology.

1. Pain

Acute iridocyclitis usually causes pain, but chronic iridocyclitis may or may not produce discomfort. The severity depends on the cause of the inflammation, type of onset, congestion, and the pain threshold of the patient.

It results from irritation of the ciliary nerves and is referred to the ocular region and periorbital area. It is aggravated by exposure to light and by pressure. If glaucoma ensues it becomes worse.

Certain types of acute iridocyclitis seem to produce more pain. Among these are herpes febrilis and zoster infections, those associated with keratitis, and those with glaucoma. It is interesting that, in herpes febrilis keratitis, pain is not severe. As soon as iritis occurs, it becomes much worse.

Chronic iridocyclitis ordinarily is accom-

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panied by dull pain, but if bullous keratopathy or keratitis develop, it becomes worse.

It is difficult to grade the severity of pain. We make an arbitrary grading of 0-4+ on the basis of the history and findings. Those patients in the 3-4+ group have severe diffuse ocular and periocular pain and usually describe a sudden onset with congestion and blurred vision. Those in the 1-2+ group have a less sudden onset, less discomfort, and only moderate congestion and blurring. The pain is often felt only in the eye itself, and is dull in character.

2. Photophobia

Photophobia usually is more severe in those patients with acute or subacute iridocyclitis. Occasional patients with chronic uveitis exhibit marked photophobia.

Quite often it is so severe that it is impossible to open the lids to examine the eye. This is especially true in children.

Photophobia in acute iridocyclitis usually is due to ciliary spasm and corneal involvement. The most severe form is seen in those cases with keratitis.

Photophobia is graded 0-4+. Such a classification, even though an arbitrary one, is worthwhile in evaluating the course of the iridocyclitis. In the more severe cases (3-4+) there is severe blepharospasm and it is difficult to examine the eye. In less severe types (1-2+) there is discomfort only in strong light. With recovery there is rapid subsidence.

3. Lacrimation

Lacrimation is not an important sign of uveitis. It is associated with photophobia, and varies much in the same manner. Patients with uninflamed eyes often have a different response to irritants and the same is true of patients with uveitis. Those with severe ciliary spasm and photophobia usually exhibit the greatest degree of lacrimation. Presumably the tearing is secondary to a reflex initiated by irritation of the corneal and ciliary nerves. It is graded 0-4+, much the same as photophobia.

4. Congestion

Circumcorneal and conjunctival inflammation is more marked in severe iridocyclitis and is dependent on extension of the uveal inflammation into and around the anterior ciliary vessels at the limbus. Very little or no congestion occurs in chronic iridocyclitis.

In less acute cases the inflammation is confined to the deep circumcorneal vessels which have a violet hue, due to their depth (fig. 1). In more severe cases it extends outward from the circumcorneal region into the conjunctiva, which becomes somewhat chemotic (fig. 2). More violent inflammations are accompanied by scleritis, episcleritis, and peripheral keratitis (figs. 3 and 4).

It is characteristic of Fuchs' syndrome of heterochromic iridocyclitis that there is an absence of circumcorneal inflammation.

Congestion is a valuable sign, indicating the progress or improvement in the intraocular inflammation. It is graded 0-4+. The following findings are recorded:

0 = No congestion.
1+ = Slight to moderate circumcorneal injection.
2+ = Marked circumcorneal ciliary injection.
3+ = Marked circumcorneal plus some dif-

Fig. 1 (Hogan, Kimura, and Thygeson). Two-plus congestion, primarily circumcorneal.

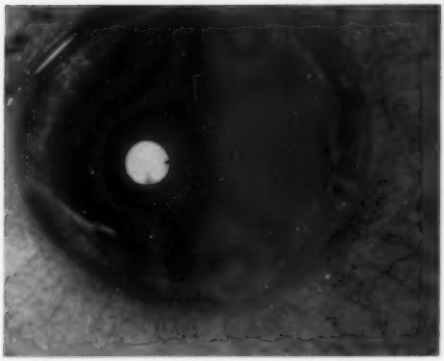

Fig. 2 (Hogan, Kimura, and Thygeson). Three-plus congestion, diffuse anterior involvement.

fuse episcleral and conjunctival congestion.

4+ = Marked circumcorneal, diffuse episcleral, and conjunctival injection with edema.

5. Blurred vision

Blurred vision in patients with acute or chronic anterior uveitis may be due to a number of causes.

In acute iridocyclitis the blurring in the early stages most often is due to the intense exudation into the anterior chamber and anterior vitreous. Exudation of cells, protein-rich fluid, and fibrin, lead to opacification of the media and reduction of acuity. At times deposition of cells and debris on the back of the cornea reduces vision. This may lead to keratitis and corneal edema, further reducing the acuity.

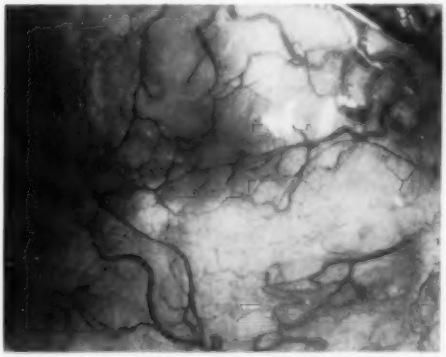

Fig. 3 (Hogan, Kimura, and Thygeson). Four-plus congestion with marked chemosis.

Fig. 4 (Hogan, Kimura, and Thygeson). Four-plus congestion showing chemosis.

Intense anterior inflammation may produce macular edema, followed by cyst or hole formation, and corresponding visual damage. Prolonged chronic inflammation, especially with heavy vitreous exudation, may do likewise. Papillitis, with edema and damage to the nerve fibers may reduce acuity. This will be discussed in Part II.

Prolonged iridocyclitis often leads to pigment deposition and proliferation of fibrous tissue from the iris onto the lens capsule, and affects vision. Acute or subacute glaucoma with corneal edema usually causes blurring.

Visual acuity is recorded in the usual manner after testing with the Snellen chart.

6. Keratitis and Keratopathy

Keratitis and keratopathy are well known complications of the various types of acute and chronic iridocyclitis. They arise in two ways:

1. By extension of the inflammation into the peripheral cornea from the limbal circulation (figs. 5, 6 and 7).

2. Through a damaged corneal endothelium and Descemet's membrane (fig. 8).

A variety of types of coincidental inflammation of the uvea and the cornea are seen:

In tuberculous iridocyclitis a segmental keratitis may occur, having a somewhat triangular shape, with its apex at the corneal center. Syphilis, especially the congenital

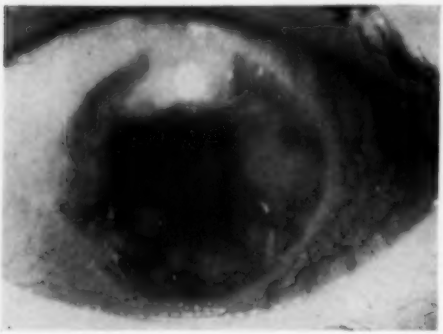

Fig. 5 (Hogan, Kimura, and Thygeson). Corneal scars, congestion, synechias in iridocyclitis of tuberculous origin.

type, often involves the cornea and anterior uveal tract almost simultaneously. "Anterior segmentitis" is commonly employed in European literature to describe a simultaneous involvement of the anterior uvea and cornea; probably secondary to a number of causes. In herpes zoster infections there may be a sudden onset of iritis and keratitis, through most often the iritis seems to be secondary. Occasional cases of herpes simplex keratitis have an almost simultaneous onset of kerato-iritis.

In young individuals iridocyclitis often leads to band keratopathy, characterized by a progressive superficial deposition of calcium in a bandlike zone across the central cornea (fig. 9). This condition may occur in any type of juvenile iridocyclitis. It has been described principally in juvenile rheumatoid arthritis (Still's disease).

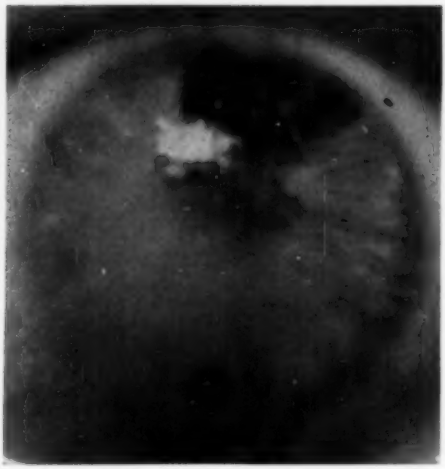

Fig. 7 (Hogan, Kimura, and Thygeson). Tuberculous iridocyclitis with secondary keratitis.

Prolonged iridocyclitis almost always leads to keratitis, with haziness and edema, folds in Descemet's membrane, and vesicle and bulla formation in the epithelium. Large keratic precipitates often produce

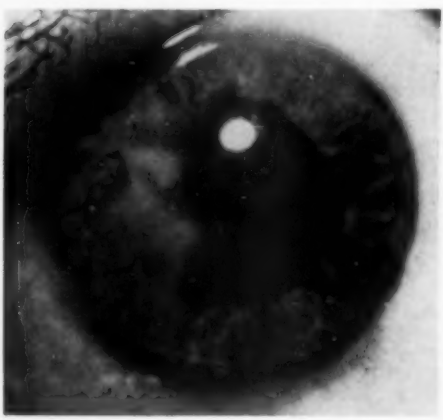

Fig. 6 (Hogan, Kimura, and Thygeson). Sclerosing keratitis and iritis.

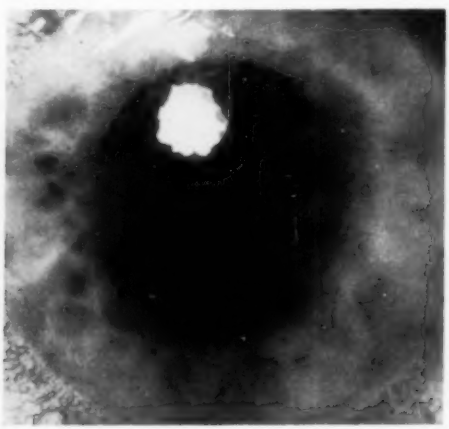

Fig. 8 (Hogan, Kimura, and Thygeson). Corneal edema due to iritis.

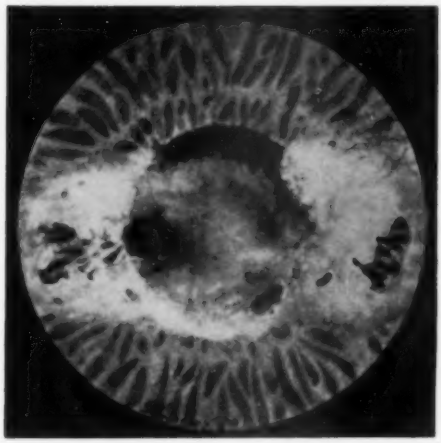

Fig. 9 (Hogan, Kimura, and Thygeson). Band keratopathy.

edema (fig. 10). Persistent edema usually is followed by pannus formation and there may be peripheral vascularization of the stroma.

The development of glaucoma favors the more rapid onset of keratopathy.

Keratitis and keratopathy are classified on a scale of 0-4+ as follows:

0 = No inflammation or edema.
1+ = Slight diffuse stromal edema.
2+ = Moderate epithelial and stromal edema, with thickening and folds in Descemet's membrane.
3+ = Diffuse epithelial and stromal edema; folds in Descemet's membrane; peripheral vascularization; beginning fibrosis in the stroma in localized areas.
4+ = Severe edema of the stroma; epithelial vesicle and bulla formation; peripheral vascularization.

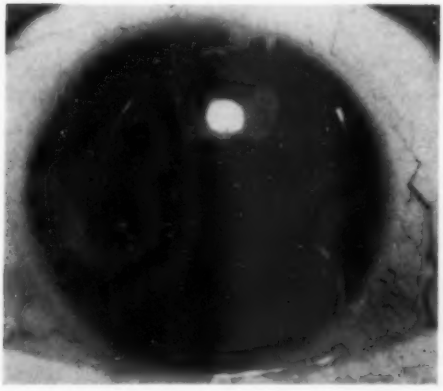

Fig. 10 (Hogan, Kimura, and Thygeson). Mutton-fat keratic precipitates with secondary edema.

7. Keratic precipitates

Keratic precipitates are deposits of inflammatory cells on the endothelium of the cornea. They occur in acute and chronic iridocyclitis, and vary in size, number, character, and position, depending on the type of uveal inflammation. They usually are found on the mid- and lower cornea, because they are deposited by the aqueous convection currents. Damage to the corneal endothelium favors deposition of these cells. Macrophages tend to adhere to each other and to the endothelium and form larger keratic precipitates. The composition of the aqueous also probably has something to do with formation of keratic precipitates. Aqueous containing fibrin and a large amount of protein circulates poorly and traps the cells, so they cannot be deposited on the cornea.

The type of cellular exudation into the aqueous humor depends on the nature of the iridocyclitis. Lymphocytes and plasma cells are most frequently found. Macrophages occur in large numbers in some types of iridocyclitis. Polymorphonuclear leukocytes and eosinophils are seen much less frequently. The composition of the keratic precipitates, therefore, varies with the severity, duration, and type of inflammation which occurs.

Keratic precipitates are ordinarily classified into the following types: (1) Mutton fat; (2) white—small, medium-sized.

Mutton-fat keratic precipitates

Mutton-fat keratic precipitates are more characteristic of chronic inflammation and are more often observed in those patients with such conditions as sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome, toxoplasmosis, tuberculosis, sarcoidosis, and

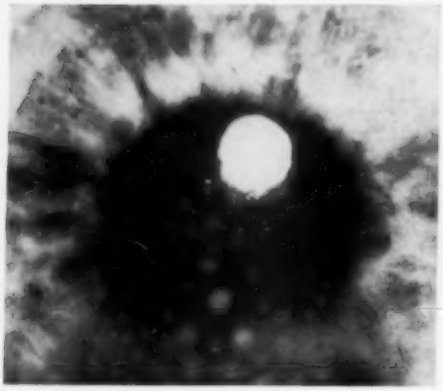

Fig. 11 (Hogan, Kimura, and Thygeson). Mutton-fat keratic precipitates in toxoplasmic chorioretinitis.

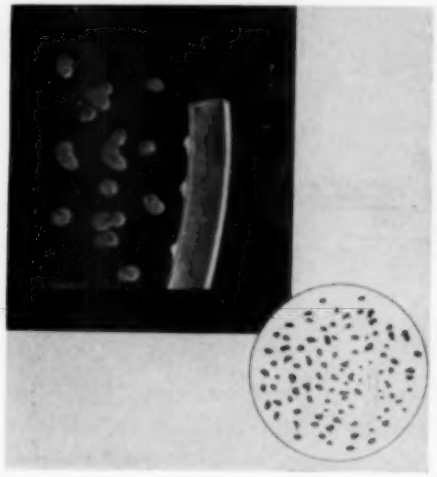

Fig. 12 (Hogan, Kimura, and Thygeson). Irregular shaped and coalescing mutton-fat keratic precipitates.

leprosy (fig. 11). Many other types of disease could be cited in which these types of keratic precipitates are observed, but in general most are of the type known pathologically as "granulomatous" diseases.

Mutton-fat keratic precipitates are rather large, tend to be small at first and increase in size by coalescence. Characteristically they lie on the mid- and lower-cornea and are moderate in number (fig. 12). They have a waxy or fatty appearance, due to their composition, and the material they have phagocytosed. They are composed of macrophages, with a small admixture of lymphocytes and plasma cells (fig. 13). Sarcoid keratic precipitates often reach large size, especially when they arise in the periphery of the cornea.

White keratic precipitates

Small or medium-sized white keratic precipitates are more characteristic of acute iridocyclitis, Fuchs' heterochromic iridocyclitis, chronic infectious types, and allergic iridocyclitis.

Fig. 13 (Hogan, Kimura, and Thygeson). Fresh large mutton-fat keratic precipitates, severe iritis.

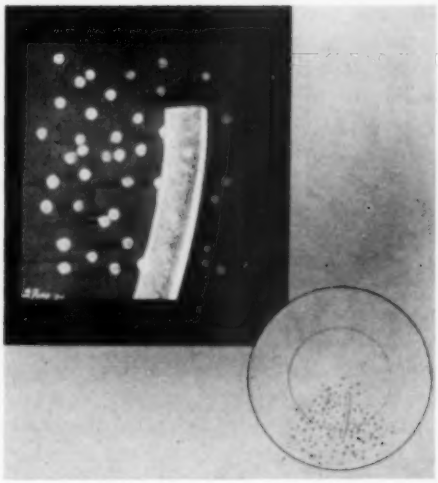

Fig. 14 (Hogan, Kimura, and Thygeson). Medium-sized round white keratic precipitates. Note distribution and lack of coalescence.

They are found on the mid- and lower cornea, are sharply defined, round, and quite white in appearance (fig. 14). They do not increase in size once they have formed, and very rarely coalesce to form larger cell masses. Acute iridocyclitis is characterized by medium-sized keratic precipitates; whereas, in Fuchs' heterochromic iridocyclitis they are smaller.

They are composed of lymphocytes and plasma cells and occasionally contain eosinophils (figs. 15 and 16). They tend to disappear rather rapidly as the disease clears, whereas mutton-fat keratic precipitates remain for long periods as somewhat pigmented deposits.

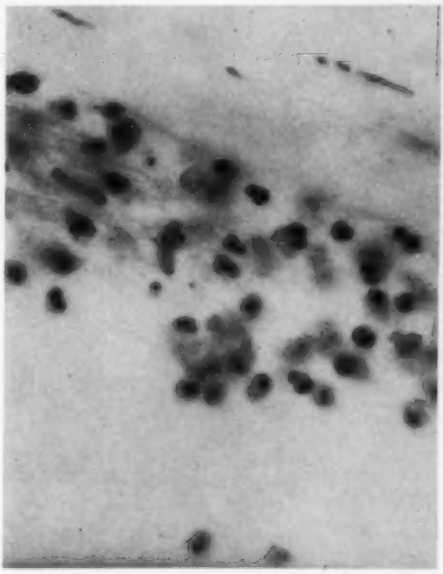

Fig. 16 (Hogan, Kimura, and Thygeson). Round white keratic precipitates, lymphocytes, plasma cells, polymorphonuclear leukocytes.

A certain amount of pigmentation is

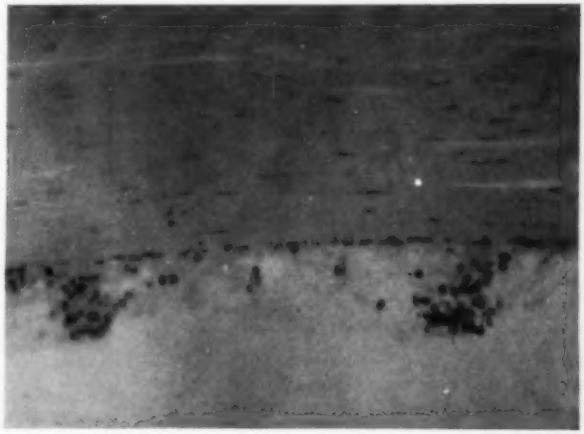

Fig. 15 (Hogan, Kimura, and Thygeson). Round white keratic precipitates, fibrin, and scattered cells.

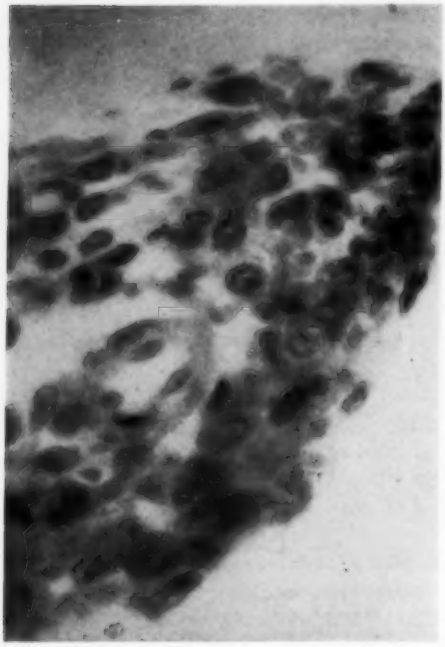

Fig. 17 (Hogan, Kimura, and Thygeson). Large, pigmented, mutton-fat keratic precipitates, mainly composed of macrophages.

common in all keratic precipitates but it is more marked in the mutton-fat type because pigment granules are phagocytized by the cells. The more severe and prolonged the disease the more likely pigment is to be phagocytized (fig. 17).

At times there is diffuse deposition of keratic precipitates on the posterior cornea (fig. 18). In such cases the distribution seems to be related somehow to the severity and persistence of the inflammation. This is much more common in herpes febrilis and zoster iridocyclitis.

Fresh white keratic precipitates have rounded smooth margins. Mutton-fat keratic precipitates have somewhat irregular margins, and as they tend to disappear they become more irregular and eventually develop scalloped or crenated edges. White keratic precipitates can disappear slowly, without becoming crenated.

Keratic precipitates should be classified according to type, size, distribution, and number. It is best to make a drawing of the position for record purposes.

8. Flare

Flare is produced by the passage of light through the protein-rich aqueous humor which forms in iridocyclitis, and is comparable to the Tyndall phenomenon. It is more intense in severe attacks, and often is faint and constant in chronic disease. As long as a flare persists in the aqueous one should assume that the inflammation is active, except in atrophic, soft eyes.

Flare is best detected by examination with the slitlamp in a very dark room. The observer should be somewhat dark-adapted. Moderate illumination through a narrow slit is employed.

The flare is graded according to its intensity. Instruments are available if one wishes to make an exact measurement. We ordinarily use the following:

0 = Complete absence.
1+ = Faint flare (barely detectable).
2+ = Moderate flare (iris and lens details clear).
3+ = Marked flare (iris and lens details hazy).

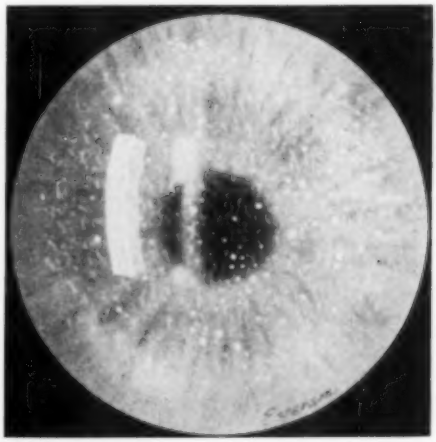

Fig. 18 (Hogan, Kimura, and Thygeson). Medium and small white keratic precipitates. Stringy deposits of cells and fibrin.

4+ = Intense flare (fixed, coagulated aqueous humor with considerable fibrin).

9. Aqueous cells

Cells from the inflammatory process in the iris and ciliary body pass either by diffusion or by active migration from the tissues into the aqueous humor. They are manufactured locally from fixed tissue cells, or pass through the capillary walls from the blood into the tissues and thence to the aqueous humor. Cells from the ciliary body pass through the epithelial layers into the posterior chamber, thence into the anterior chamber and vitreous.

They leave the eye via the angle structures or are removed by the uveal circulation. Many cells undergo lysis. Examination of these cells after aspiration of aqueous humor frequently shows extensive degenerative changes.

The number of cells which are visible in the aqueous humor with the slitlamp microscope depends on the severity of the inflammation, and degree of flare present.

Different types of cells can be detected by slitlamp examination. The following are commonly seen:

1. *Inflammatory.* The types usually seen in iridocyclitis are lymphocytes and plasma cells. They are small, spherical, glistening, and unpigmented. They move with varying speed. They are more difficult to see when there is an intense flare, and again appear as the flare decreases. We cannot emphasize too much the necessity of good light for detection of aqueous cells, especially when they are present in small numbers.

2. *Macrophages.* These are more easily recognized by their larger size, especially when they are full of ingested material, such as lens debris and pigment.

3. *Pigment cells and granules.* Are usually detected by their small size and color. They are found in those cases showing pigment destruction or liberation. Other pigment cells may be large macrophages which have phagocytized uveal or blood pigment.

Irvine and Irvine[2] have described the frequent misinterpretation of particulate matter for cells, especially in patients with hypermature cataract.

We grade cells according to number observed in slitlamp microscope fields (wide beam with narrow slit).

0 = No cells.
1+ = 5 to 10 cells per field.
2+ = 10 to 20 cells per field.
3+ = 20 to 50 cells per field.
4+ = 50+ cells per field.

10. Anterior chamber angle, iris, and lens precipitates

White and mutton-fat keratic precipitates may be seen on the trabecular meshwork, in the angle, on the surface of the iris, and on the lens (figs. 19 and 20). The deposition of these clusters of cells occurs in the same manner as on the back of the cornea and has the same significance.

Precipitates of this type most often occur in patients with severe, prolonged iridocyclitis or in long-standing chronic iridocyclitis. Therefore, the finding of precipitates in areas other than the back of the cornea has a more grave prognostic significance. Some iris precipitates are called "Koeppe nodules" and "Busacca nodules." These structures are more properly precipitates because they are composed of agglomerated cells at the pupil margin or on the iris surface.

We ordinarily are content with a description of the presence of precipitates in areas other than the back of the cornea, and indicate the position and number seen.

11. Clot (fibrin)

At times there is coagulation of the exudate in the aqueous humor. It usually occurs in those cases of acute severe iridocyclitis which have a sudden onset and is due to an excessive amount of fibrin in the anterior chamber.

The clot is classified as to amount:

0 = No clot.
1+ = A small clot in lower angle or pupillary area.

Fig. 19 (Hogan, Kimura, and Thygeson). Mutton-fat precipitate on trabeculae.

2+ = A clot occupying lower third of anterior chamber.
3+ = A clot filling lower half of anterior chamber.
4+ = A solid clot filling almost the entire anterior chamber.

12. Iris nodules

Iris nodules are produced by infiltration of inflammatory cells, usually lymphocytes and plasma cells, into the stroma (figs. 21 and 22). They commonly lie in the pupillary zone, but may occur elsewhere in the stroma. At times they are seen in the stroma of the pupillary portion in which case they are due either to proliferation of the iris epithelium,

Fig. 20 (Hogan, Kimura, and Thygeson). Sarcoid nodule in the angle.

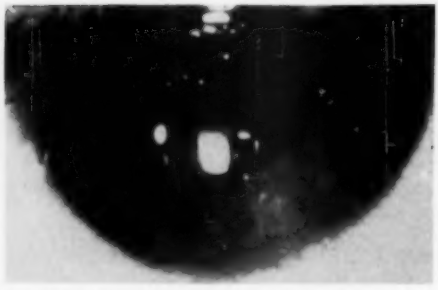

Fig. 21 (Hogan, Kimura, and Thygeson). Iris nodule. Probably sarcoid.

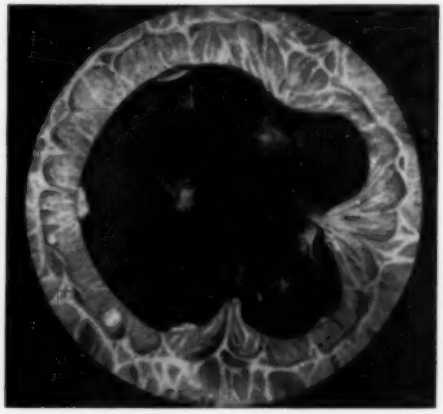

Fig. 22 (Hogan, Kimura, and Thygeson). Pupillary nodules and iris precipitates.

or infiltration with round cells and macrophages (fig. 23).

Rarely such nodules are typical granulomatous lesions, such as miliary or conglomerate tubercles, sarcoid nodules, nodules of leprosy, or those occurring in other granulomatous diseases.

The usual nodule is found in chronic iridocyclitis, may be transient or persistent, and most often is formed of lymphocytes and plasma cells. Following healing there is no scar. Granulomatous lesions are usually larger, more elevated, and persist longer. Subsidence is accompanied by hyalinization, scar formation, or severe focal atrophy (fig. 24).

It is difficult to assess the importance of nodule formation. Most often the nodules are associated with chronic disease, the nature of which cannot be determined. Occasionally a presumptive diagnosis of tuberculosis, syphilis or sarcoidosis can be made,

Fig. 23 (Hogan, Kimura, and Thygeson). Pupillary nodules.

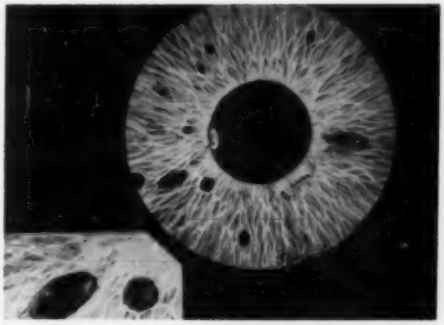

Fig. 24 (Hogan, Kimura, and Thygeson). Focal atrophy with hyalinization following iris nodules.

and the diagnosis can be confirmed on clinical study.

Some patients with chorioretinitis show a reactive iris inflammation with nodule formation. The nodules are predominantly lymphocytic, and this type of change is common in toxoplasmosis.

Nodules at times develop in the iris root, stroma of the ciliary body, or uveal meshwork. If they coalesce or increase in size they become visible as rather large masses in the angle.

We diagram all nodules, indicating their position, size, color, and vascularity. They must be distinguished from iris precipitates, which lie on the surface of the iris.

13. Hemorrhage

Some types of iritis cause bleeding into the anterior chamber. Ordinarily the hemorrhage is small and occupies the lower one-fourth to one-third of the anterior chamber. Absorption is rapid if the outflow channels are patent. If there is trabecular obstruction absorption may be delayed.

Some types of iritis are thought to be more likely to produce hemorrhage, for example, gonorrheal iritis. In our experience herpetic iridocyclitis is a much more common cause. The exact reason for development of hemorrhage in some cases of iritis is unknown, and it seems to have no particular etiologic or prognostic significance.

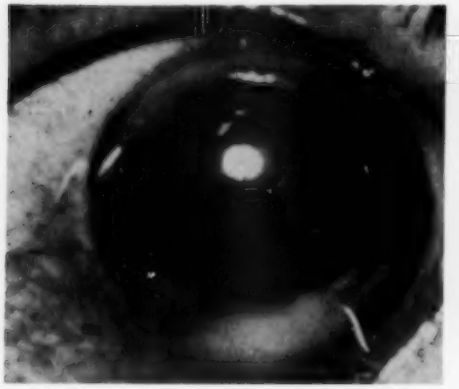

Fig. 25 (Hogan, Kimura, and Thygeson). Hypopyon in Behçet's syndrome.

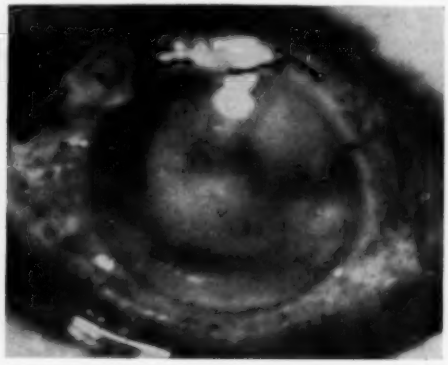

Fig. 26 (Hogan, Kimura, and Thygeson). Lens induced inflammatory exudate. Cultures negative. Same reaction opposite eye. Excellent outcome.

Because of the infrequency of hyphema in iridocyclitis and its lack of significance, we ordinarily are content with making a record of its presence and degree.

14. Hypopyon

Hypopyon is uncommon in acute iritis. Presumably it most often results from the acute inflammation produced by an infectious agent, but proof is lacking, except in rare cases.

A typical example of hypopyon iridocyclitis is that seen in Behcet's disease (fig. 25). Recurrences of iritis over a period of months or years eventually lead to attacks with hypopyon formation and eventually to loss of vision. The hypopyon rarely occupies more than the lower chamber, and often disappears within two to five days.

Other types of hypopyon uveitis occur spontaneously and often are nonrecurrent. The etiology usually is undetermined. Lens induced inflammations often lead to formation of purulent exudate (figs. 26 and 27). The hypopyon is classified according to amount and position.

15. Iris atrophy

Iris atrophy results from prolonged inflammation in the stroma and epithelium of the iris. The atrophy may be diffuse, irregular, patchy, or focal in type.

Fibrosis and scarring as a result of prolonged chronic inflammation leads to smoothing of the normal iris pattern. The development of synechias leads to immobilization with a sector-shaped stretching of the stroma and pigment layer, and further atrophy.

Patchy areas of atrophy are characteristic of iridocyclitis in which there is nodule formation. Healing of the nodule results in formation of a scar which may shrink.

The following types of atrophy are seen:

1. *Inflammatory.* Inflammatory atrophy

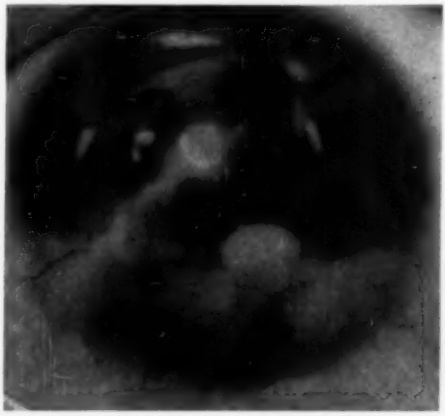

Fig. 27 (Hogan, Kimura, and Thygeson). Traumatic cataract, for two years. Hypopyon due to lens reaction.

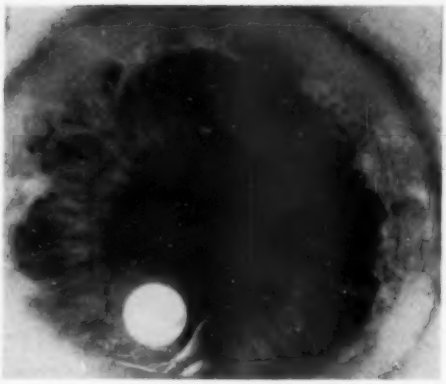

Fig. 28 (Hogan, Kimura, and Thygeson). Diffuse *stromal* atrophy characteristic of long-standing iritis.

involves both the stroma and pigment layer, at times more marked in one than in the other of these two layers (fig. 28). The characteristics and causation have already been discussed.

2. *Heterochromic iridocyclitis.* In this type of iridocyclitis there is atrophy of the pigment epithelium in the pupillary zone of the iris (fig. 29). This is best detected by transillumination, which shows numerous depigmented areas. The stroma also shows depigmentation and a moderate amount of thinning

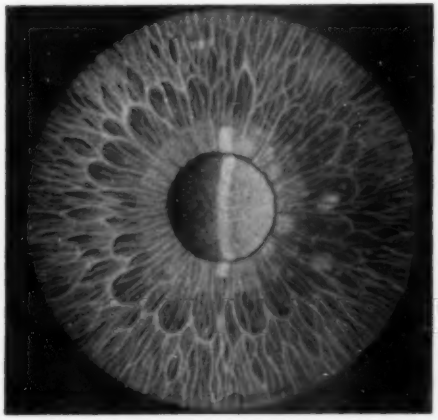

Fig. 29 (Hogan, Kimura, and Thygeson). Pigment atrophy characteristic of heterochromic iridocyclitis.

Fig. 30 (Hogan, Kimura, and Thygeson). Iris pigment atrophy in heterochromic iridocyclitis.

of the anterior trabecular pattern (fig. 30).

3. *Focal.* In some viral diseases such as herpes zoster and herpes febrilis, localized acute inflammation and swelling occurs in the stroma (fig. 31). On subsidence a circumscribed small area of atrophy persists. These zones of atrophy frequently measure two to three mm. in size. Rarely, they are somewhat larger.

16. Synechias

Synechias ordinarily form in iridocyclitis cases which are characterized by heavy exudation of a protein-rich fluid, causing adhesion of the iris to the lens. Inflammatory cells and fibroblasts from the iris then lead to organization of the adhesions (figs. 32 and 33).

Synechia formation is variable in uveitis, some patients having as many as 20 to 30 attacks without developing adhesions; others have one severe attack and form extensive adhesions. At times they form when the pupil is small, leading to occlusion and seclusion, and in other instances they form

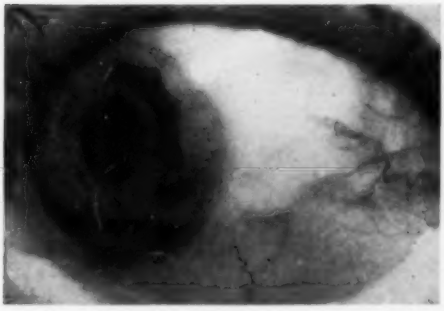

Fig. 31 (Hogan, Kimura, and Thygeson). Focal iris atrophy following herpes zoster.

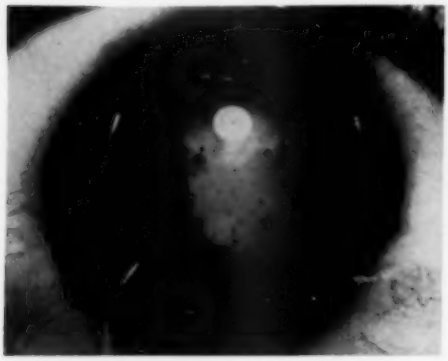

Fig. 32 (Hogan, Kimura, and Thygeson). Synechias and cataract due to iridocyclitis.

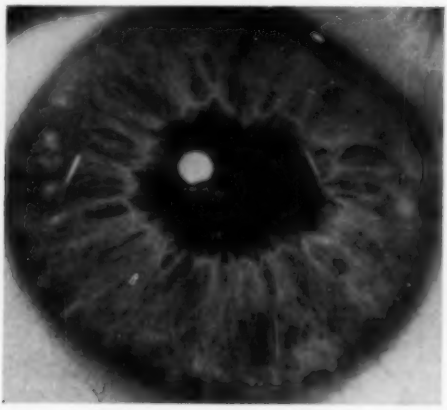

Fig. 33 (Hogan, Kimura, and Thygeson). Chronic iridocyclitis. Synechias. Iris atrophy.

when the pupil has been kept dilated. In rare cases the entire posterior surface of the iris becomes firmly adherent to the surface of the lens, and, even though glaucoma occurs, iris bombé does not develop. Chronic iritis is much more likely to produce adhesions than repeated short-lived acute attacks.

Peripheral anterior synechia formation depends on several factors:

1. Shallowing of the anterior chamber as a result of pupillary block.

2. Organization of inflammatory exudate in the angle with gradual attraction of the iris toward the angle structures (fig. 34).

3. Intense edema and swelling of the root of the iris. Gonioscopic observations by us in a fair number of patients show that peripheral synechia formation is not an early manifestation or prominent feature in iridocyclitis.

Some types, such as the Fuchs' heterochromic type, never develop synechias. Flare ordinarily is minimal in these cases, therefore there is almost no tendency for the iris to become adherent to the lens or to the trabecular area.

Synechias are designated by making drawings of the pupillary region and indicating their extent and character. The same is done to show peripheral anterior synechias.

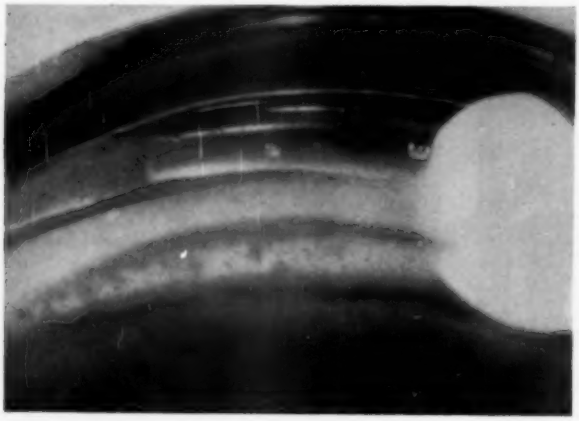

Fig. 34 (Hogan, Kimura, and Thygeson). Small peripheral anterior synechias in iritis.

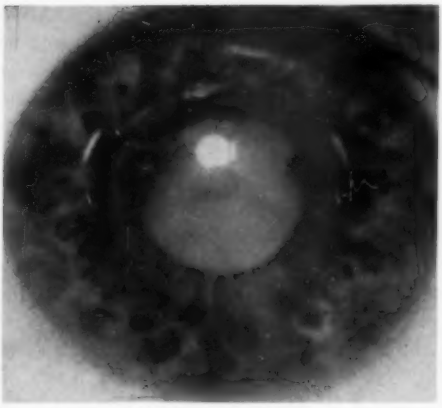

Fig. 35 (Hogan, Kimura, and Thygeson). Synechias and cataract due to iridocyclitis.

Fig. 37 (Hogan, Kimura, and Thygeson). Anterior cataract in iridocyclitis.

17. The lens

Cataract formation results from the toxic effects of the uveal inflammatory process. That in the anterior lens is due to toxic damage to the epithelium and cortex or to synechia formation. Damage to the anterior lens epithelium leads to degenerative and proliferative changes, and to liquefaction of the superficial lens fibers (figs. 35, 36, and 37).

Long-standing, persistent cyclitis almost invariably leads to degenerative changes in the cortical fibers beneath the posterior capsule (figs. 38 and 39). (Cataract due to cyclitis in preference to cataracta complicata.)

Some patients with severe cyclitis develop widespread changes in the lens, both in the anterior and posterior cortex, with rapid formation of a complete cataract.

Lens changes should be designated in the record by drawings, both in the frontal plane as well as in the sagittal to indicate their site, size and character.

Fig. 36 (Hogan, Kimura, and Thygeson). Band keratopathy, synechias, cataract, due to iritis.

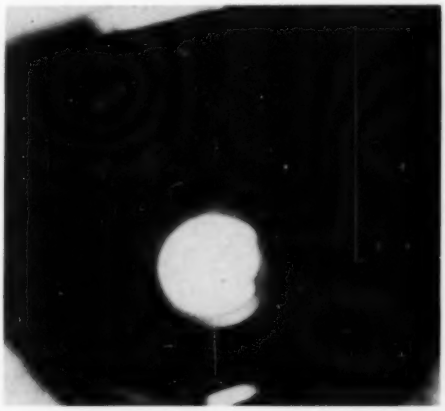

Fig. 38 (Hogan, Kimura, and Thygeson). Posterior subcapsular cataract due to cyclitis.

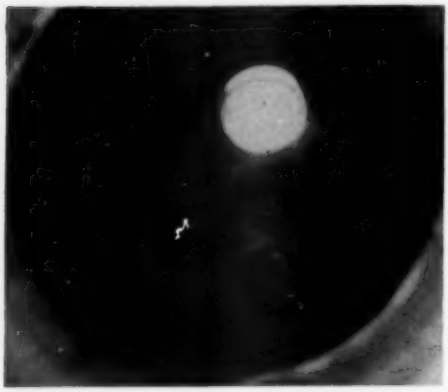

Fig. 39 (Hogan, Kimura, and Thygeson). Posterior subcapsular cataract in cyclitis.

18. Intraocular pressure (glaucoma and hypotony)

A *low* tension is characteristic of uveitis, especially the acute varieties. The lowered tension is due to decreased production of aqueous humor. The exact method by which this occurs is not known.

Glaucoma in anterior uveitis may develop as an early or late manifestation. Early glaucoma usually is due to obstruction of the outflow channels by an actual inflammatory process in the trabecula or anterior ciliary body. At other times it is due to clogging of the trabecular spaces and Schlemm's canal by cellular debris and exudate.

Late glaucoma is due to the sequelae of prolonged inflammation which produces degeneration and fibrosis of the trabecular fibers and narrowing or closure of the smaller openings in the region of Schlemm's canal. At other times it is due to formation of peripheral anterior synechias.

In acute iridocyclitis the trabecular spaces most often are infiltrated with round cells, coagulated protein, and debris. Outflow studies frequently show an obstruction to outflow of aqueous humor, but glaucoma does not develop because there is a coincident diminution in production of aqueous humor.

In glaucomatocyclitic crises and some types of iritis resembling this condition, the initial inflammatory process is thought to lie within the ciliary body close to the trabecular meshwork. The intensity of the inflammation causes obstruction to outflow, and glaucoma. As the inflammatory process spreads backward into the stroma of the ciliary body it causes diminished production of aqueous humor, and the tension falls. At the same time there is exudation of inflammatory cells into the aqueous humor, and the signs of iridocyclitis appear.

Patients with chronic iridocyclitis, controlled with steroid therapy, at times develop glaucoma, which is relieved by reducing or discontinuing therapy. Recurrence of the iritis probably accounts for this reduction in pressure.

The intraocular pressure should be measured regularly in patients with chronic iridocyclitis.

Summary and Conclusions

1. The signs and symptoms of anterior uveal inflammation are described and their pathogenesis and significance discussed.

2. A method of recording the intensity and character of some of the signs is presented. The necessity for development of a uniform system of recording these signs is discussed.

University of California Medical Center (22).

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SIGNS AND SYMPTOMS OF UVEITIS*

II. Classification of the posterior manifestations of uveitis

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General agreement on the classification of the various signs of uveitis in the posterior segment of the eye was difficult to achieve in the early phase of our uveitis survey studies. After observations and discussion we were able to agree on the findings and assess the significance of the various signs. This classification has been extremely helpful to us in clinical studies as well as in evaluating the progress of the disease in our patients.

1. Vitreous opacities

The vitreous is involved with considerable frequency in uveitis. The changes reflect the degree, and, to a certain extent, the position and character of the inflammation in the uveal tract.

Inflammatory cells, red blood cells, tissue cells, and a protein-rich fluid permeate the vitreous in uveitis and cause a variable amount of cloudiness. The changes seen with the slitlamp microscope and ophthalmoscope depend on the amount and type of exudation.

Vitreous opacities are classified according to size, characteristics, and position.

Fine opacities. These are composed of clumps of cells, debris, coagulated exudate, and fibrin. The cells are predominantly lymphocytes, plasma cells, and macrophages.

Coarse opacities. Those opacities are large and irregular and more often are seen in severe, destructive lesions of the posterior segment. They are composed of tissue cells, macrophages, and fibrin clumps.

Stringy opacities. These are seen in more severe and long-standing posterior segment uveitis. They are present along with fine cellular and coarse fibrin opacities. Stringy vitreous opacities are probably due to alteration of the vitreous itself.

Snowball opacities. These are rather large, round, glistening, gray opacities suspended in the peripheral vitreous, usually posteriorly. Even though this term "snowball opacities" was first used to describe asteroid hyalitis, for want of a better term we choose to use it here. They are rather uncommon and are seen occasionally in cases with large diffuse chorioretinal lesions where they are thought to be similar to "mutton-fat" keratic precipitates. Their makeup or significance is unknown. They have been described in cases of Boeck's sarcoidosis,[1] although we do not believe they are specific for this disease.

Ophthalmoscopically all vitreous opacities (except red blood cells and pigment) are white or gray-white in color when seen by reflected light and appear dark when seen in retroillumination against the background of the fundus and optic disc. They are best studied with the slitlamp microscope. As commonly used only three or four millimeters of the anterior vitreous can be seen, but by the use of contact lens the entire vitreous structure can be examined. Figure 1 shows a drawing of the slitlamp view of an active chorioretinitis seen through a contact lens.

Vitreous exudate from a uveal inflammation, as in plasmoid aqueous humor, gives a positive Tyndall effect when viewed with a narrow slit (fig. 1). As long as the chorioretinitis is active this flare is present. If the

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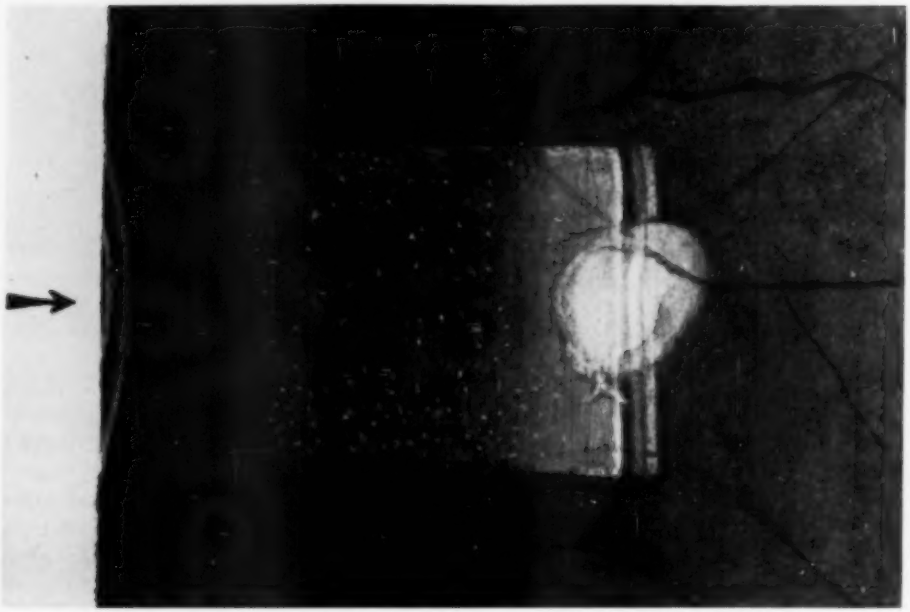

Fig. 1 (Kimura, Thygeson, and Hogan). Slitlamp view of posterior eye with chorioretinitis seen through a contact lens.

vitreous is detached, one also observes a flare in the retrovitreal space. The inflammatory cells can be visualized as to their size and position in the vitreous. In iridocyclitis or cyclitis they are seen in the anterior vitreous, whereas in chorioretinitis they are usually located in the posterior portion (fig. 1). These opacities usually are freely moveable. After the chorioretinitis has subsided the vitreous opacities usually persist for many weeks.

Vitreous opacities are classified as follows:

0—No opacities.
+—Few scattered fine and coarse opacities. Fundus clearly seen.
++—Scattered fine and coarse opacities but fundus details somewhat obscured.
+++—Many opacities with marked blurring of fundus.
++++—Dense opacities which prevent a view of the fundus.

It should be recorded whether the opacities are predominantly anterior or posterior.

2. Vitreous detachment

Vitreous detachment is a common finding in cases of severe iridocyclitis and chorioretinitis. Liquefaction and shrinkage due to the exudation from the inflammation plays a definite role. Goldmann[2] described posterior vitreous detachment with or without collapse of the vitreous structure. However, vitreous detachment without collapse is rare. Detachment with collapse is common in uveitis as it is preceded by degeneration of the vitreous due to the severe uveal inflammation. Frequently in uveitis one finds cellular precipitates on the detached posterior hyaloid membrane. The retrovitreal space usually is filled with a liquid containing cells and exhibiting a flare as long as there is an active uveal inflammation. When the vitreous is detached from the optic disc, a ring opacity can often be seen in the midportion of the eye with the ophthalmoscope.

Late detachment of the vitreous in uveitis may be due to shrinkage. During this

stage if vitreoretinal bands have formed, retinal holes may develop with subsequent retinal detachment.

Slitlamp examination with a contact lens (Goldmann's three mirror lens) is the best way to study the vitreous. The extent of the posterior detachment as well as the presence of cells and flare should be noted in every case of uveitis.

In most cases vitreous detachment is of little significance except for the annoying opacities that are seen entoptically. However, there is a definite relationship between vitreous detachment and subsequent retinal detachment in these cases. Therefore any eye showing vitreous detachment, especially if it develops late in convalescence, should be examined closely for retinal holes and early retinal detachment.

It is best to describe the location and the extent of the vitreous detachment by a sketch in the record.

3. Macular edema

Retinal edema is a common finding in uveitis. The posterior pole is especially involved and is particularly marked at the nervehead and the macula.

Macular edema is often responsible for the decreased visual acuity that is seen in cases of anterior uveitis. Prolonged edema of the macula leads to cystic degeneration and permanent loss of vision.

Duke-Elder[3] states that excessive retinal edema may cause a local exudative detachment of the central area (discussed under retinal detachments).

No attempt is made to grade the amount of edema that is present in every case. Only the presence of edema is noted in our work-up of uveitis cases.

4. Optic nerve changes

Swelling of the optic disc is a common accompaniment of severe iridocyclitis or chorioretinitis. The papillitis is due to the irritative effects of the inflammation on the optic disc tissues. When the chorioretinitis is near the optic disc the papillitis is more severe. In Jensen's choroiditis juxtapapillaris the inflammation may be so severe that the retina becomes swollen and completely opaque. In such cases the choroiditis often remains unrecognized and an incorrect diagnosis of primary optic neuritis is made. Generally the papillitis is more marked in severe cases of uveitis.

Lesser degrees of swelling of the optic disc are more easily recognized. The edematous retina around the optic disc is thickened and slightly opaque. The vitreous immediately anterior to the inflamed disc shows the presence of inflammatory cells. These changes are seen best through a slitlamp microscope.

Even though most cases of papillitis associated with uveitis are transitory and leave little permanent damage, the presence and degree of swelling of the optic disc should be noted. In long-standing chronic cases the optic nerve involvement is more severe and results in a permanent damage to vision. We note by diagram the location of the swelling of the optic nervehead and presence or absence of vasculitis. The presence of a papillitis is an unfavorable prognostic sign.

5. Chorioretinitis

Active chorioretinitic lesions usually are seen as grayish-white areas. They differ, however, as to size, whether they are deep or superficial, and whether they are well circumscribed or not. We have found it convenient to classify chorioretinitic lesions as diffuse or localized and deep or superficial.

Diffuse. Diffuse chorioretinal inflammatory foci vary in size and are poorly defined (fig. 2). They are grayish or yellowish in color, and involve a number of areas of the fundus. Vitreous haze is often marked and the lesions ordinarily cannot be seen clearly during the acute phase of the disease.

Localized. Localized chorioretinal inflammatory lesions are smaller, more or less well circumscribed, and may be mild or severe (fig. 3). Vitreous haze usually is

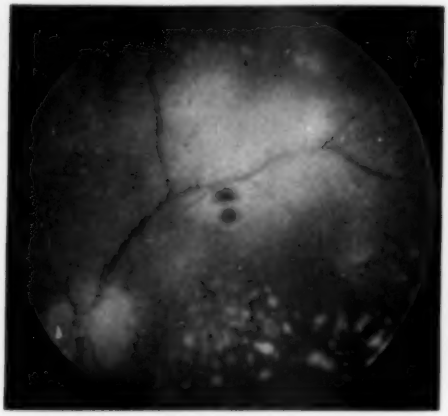

Fig. 2. (Kimura, Thygeson, and Hogan). Diffuse chorioretinitis.

less marked than in the diffuse type, although some severe forms show marked haze.

Deep. These lesions are obscure because the inflammation is deep in the choroid. Therefore there are fewer inflammatory cells thrown out into the vitreous. With the slitlamp the retina can be seen to be somewhat edematous and opaque over the deep choroidal lesion.

Superficial. Choroidal inflammation involving the inner layers produces more marked retinal inflammation and results in production of a dense vitreous haze. Such

Fig. 3. (Kimura, Thygeson, and Hogan). Localized chorioretinitis.

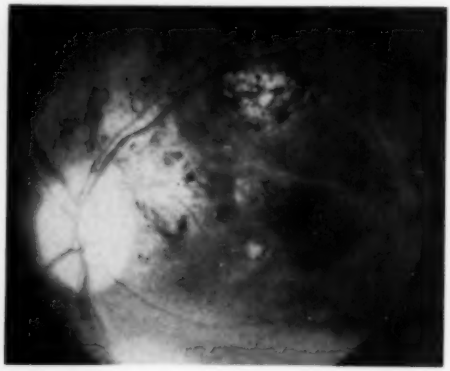

Fig. 4. (Kimura, Thygeson, and Hogan). Healed chorioretinitis showing satellite lesions.

lesions, therefore, are not clearly defined. Commonly there is exudation along the retinal blood vessels and on the posterior surface of the detached vitreous. By slitlamp examination the retina is seen to be elevated, swollen, and opaque.

Satellite. Satellite inflammations occur in the vicinity of an old healed lesion (fig. 4). These are usually smaller than the original inflammatory area. Characteristically there is a small zone of normal appearing fundus between the old scar and the new lesion.

Pigmentation of the chorioretinal lesion is a late change that occurs during healing. Severe lesions produce little pigmentation, probably because they are so severe the pigment cells are destroyed. Less severe lesions usually show more pigmentary reaction.

Chorioretinitic inflammations are best studied by slitlamp biomicroscopy. The contact lens allows the lesions to be well visualized and it is extremely valuable in noting the changes on healing.

We have not been able to establish a correlation between the appearance of chorioretinal lesions and the various known etiologies except for the satellite lesions which probably are more characteristic of recurrent toxoplasmic chorioretinitis.

6. Retinal detachment

Retinal detachment is a fairly common,

Fig. 5. (Kimura, Thygeson, and Hogan). Peripheral retinal detachment in Vogt-Koyanagi-Harada's disease.

although not often diagnosed, finding in cases of severe uveitis. The detachment is usually due to retroretinal serous exudation from the choroid. Often a hole cannot be found and the detachment heals spontaneously with the uveitis. We recognize two types of detachment:

1. *Macular detachment* is often present in cases of severe iridocyclitis. This is a flat detachment and often difficult to see because of the edema and hazy media. Most cases heal without sequelae but when the detachment and edema are of long standing the macula undergoes cystic degeneration, producing a permanent decrease in vision.

2. *Diffuse detachment* in association with a uveitis is characteristic of Vogt-Koyanagi-Harada's disease (fig. 5). It is also seen

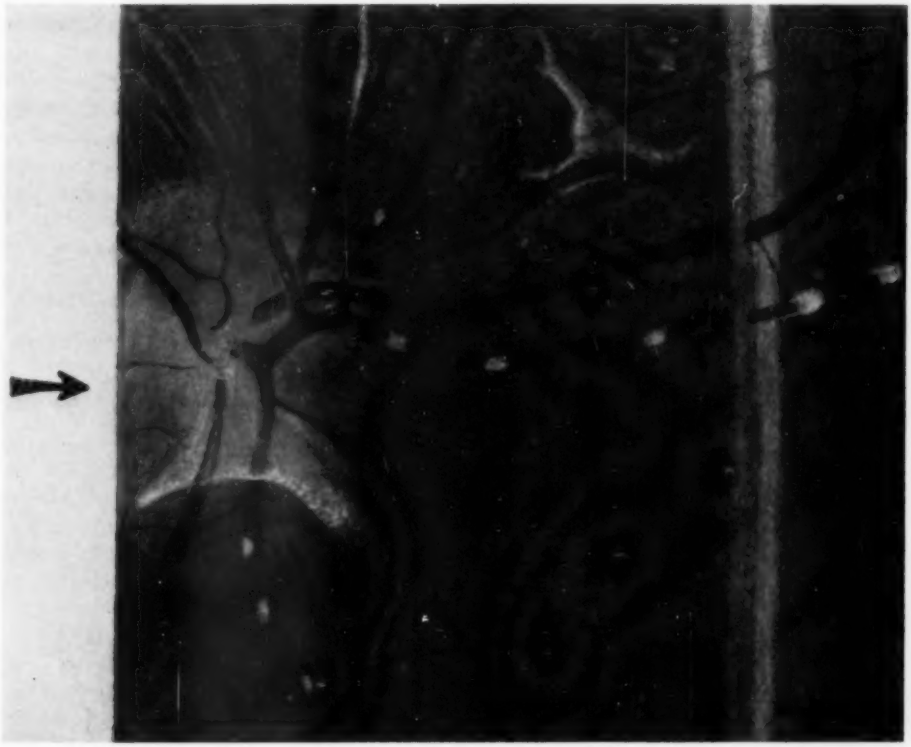

Fig. 6 (Kimura, Thygeson, and Hogan). Case with chorioretinitis (same case as in Figure 1), showing cellular infiltration along vessels.

in other forms of uveitis as herpes zoster,[4] as yet poorly understood. A serous detachment occurs and usually there is a spontaneous reattachment. The visual prognosis is usually good.

Diffuse detachment with a hole is seen as a late complication of uveitis. The hole may be formed by contraction of vitreous bands, especially a cyclitic membrane.

It is important to examine the fundus carefully in every case of uveitis because iridocyclitis may be secondary to a retinal detachment. Several cases have been referred to us as uveitis cases which proved to be primary detachments.

The use of Goldmann's three mirror contact lens should be emphasized. It is possible to study the peripheral fundus binocularly by this method and very small holes can be identified.

7. Perivasculitis

Perivasculitis is not a common finding in uveitis. The vasculitis is usually of a secondary type when it is present and in iridocyclitis it may occur rarely by retrograde extension of the inflammation of the ciliary body to the peripheral retina, involving the venous system, in many cases as far back as the equator. After subsidence of the disease perivascular venous sheathing and retinal atrophy are seen. Saccular swellings and neovascularization are common.

A more common occurrence of perivasculitis is in cases of chorioretinitis where there is cellular infiltration along the retinal vessels in the vicinity of the uveal lesions (fig. 6). The vessel sheathing is usually marked but hemorrhage rarely is seen as in primary perivasculitis. Occasionally the exudation along the vessels may be so severe as to cause occlusion of the vessel. Blood vessels in the region of a chorioretinal lesion always show some perivascular cellular infiltration.

Conclusion

The various signs of posterior uveitis have been coded and discussed. Most definitions given are not new. This discussion of basic facts is considered to be important, for without universal agreement on the terminology, proper communication would be difficult.

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THE PATHOGENESIS OF THE GLAUCOMA FIELD*

Clinical evidence that circulatory insufficiency in the optic nerve is the primary cause of visual field loss in glaucoma

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It has long been suspected that the optic atrophy and the associated visual field defects which occur in established cases of chronic simple (open-angle) glaucoma are directly related to the rate of blood flow in the optic nerve.

In 1939 to 1942, while studying the correlation between visual field loss and systolic and diastolic blood pressure, as measured in the central retinal artery on the optic disc by the Bailliart and Kukan ophthalmodynamometers in a variety of conditions, I made the clinical observation that those patients with glaucoma who exhibited the most extensive and rapid loss of visual field were the ones with generalized arteriosclerosis, low brachial and retinal arterial blood pressure, and increased intraocular pressure, sometimes of only moderate degree. Conversely, a relatively slow rate of visual field loss could be expected in an individual with increased intraocular pressure if the systemic and retinal arterial blood pressure was elevated and arteriosclerotic changes were minimal in degree.

This study was interrupted by World War II and only resumed in 1955. It is the purpose of this paper to present three different observations, each of which seems to contribute further evidence to support the theory that arterial insufficiency and decreased blood flow in the optic nerve is the primary cause of visual field loss in glaucoma. Some of the very considerable literature on vasogenic factors in glaucoma will be cited in support of this evidence.

Three patients with chronic glaucoma and arterial hypertension were observed for long intervals of time. They had not demonstrated any significant variation in their slightly elevated, but adequately controlled intraocular pressure and there were no changes in their normal or stable visual fields. Retinal arterial blood pressure paralleled the consistently elevated brachial artery blood pressure. Following marked reduction in systemic and retinal arterial blood pressure, by means of derivatives of Rauwolfia Serpentina, there was immediate and rapid deterioration in the visual fields consisting of the development of nerve fiber bundle defects (Bjerrum scotoma), peripheral depression, and nasal step. These changes in the visual fields were too rapid and profound to be accounted for by the slowly progressing optic atrophy, usually credited with advancing field loss. The only change in the patient's condition was the marked drop in blood pressure. Subsequent elevation of the brachial and retinal arterial blood pressure in one patient, by withdrawal of the depressant medication, resulted in partial restoration of the visual field loss.

On the basis of these observations, it is believed that visual field loss in these patients is the result of a relative arterial insufficiency with decreased blood flow in the arterioles of the optic nerve.

In most eyes with chronic glaucoma the circulatory deficiency results from sustained increase in intraocular pressure acting to compress the arteries of the optic disc and slowing blood flow by back pressure in the ring of Zinn-Haller.

In cases of pseudoglaucoma or low-tension glaucoma the same decrease in blood flow is effected by arteriolar sclerosis and partial occlusion of the optic nerve vessels. Little or no elevation of intraocular pressure

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is required to produce the arterial insufficiency and hypoxia in the nervehead which results in cavernous atrophy and the classical visual field defects seen in chronic glaucoma with high intraocular pressure.

In the eyes under discussion the systemic and ophthalmic arterial hypertension is sufficient to offset the moderate elevation in intraocular pressure. This balance between intraocular pressure and arterial pressure in the arterioles of the optic nerve prevents the optic nerve hypoxia necessary to the production of the typical visual field loss seen in glaucoma. When this balance is upset, either by an increase in intraocular pressure or a marked and sudden decrease in intra-arterial pressure, the result is arterial insufficiency, decrease in blood flow in the optic nerve arterioles, and rapid deterioration in the visual field.

Case reports

Case 1 (figs. 1 and 2)

Mrs. B., aged 65 years, complained of moderate decrease in reading vision not materially improved by a change of glasses. Vision was 20/25 in each eye. There was moderate lens sclerosis and very early bilateral senile macular degeneration sufficient to account for the visual complaint. Both optic nerveheads were moderately cupped with prominent cribriform fascia, but with a rim of normal tissue and slight nasal displacement of the vessels. Visual fields showed consistent superior baring of the blindspot on the right, but the left field was normal (fig. 1).

Gonioscopy showed open angles in each eye. Schiøtz tonometer readings were 2.5/5.5 in the right eye and 4/5.5 in the left eye. Retinal diastolic pulse was obtained with 55-gm. pressure with the Bailliart ophthalmodynamometer. Retinal arterial collapse was obtained with 110-gm. pressure. Brachial blood pressure was 230-240/110 mm. Hg. The retinal arteries showed considerable generalized narrowing, with venous compression at the arterial crossings and with some areas of localized narrowing. There were no hemorrhages or exudates.

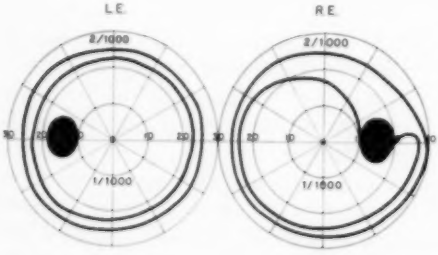

Fig. 1 (Harrington). *Case 1.* Superior baring of the blindspot in the right eye; left field, normal.

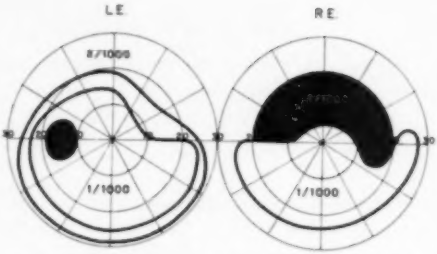

Fig. 2 (Harrington). *Case 1.* A nasal step in the right eye and depression of the superior nasal field in the left eye.

The patient was given one-percent pilocarpine drops for use in each eye twice daily. There was an immediate drop in intraocular pressure to 4.5/5.5 in the right eye and 5/5.5 in the left eye, and this was maintained for six months with readings taken at different times of the day. At the end of this time there was noted a slight rise in afternoon pressure to 3/5.5 in each eye and pilocarpine was prescribed at four-hour intervals. Under this regime the intraocular pressure was measured at frequent intervals and tonometer readings averaged 3.5/5.5 with occasional readings of 2.5/5.5 to 4/5.5. There was no apparent change in the optic disc and the visual fields remained stable on repeated testing for the next year and a half.

The patient knew that her blood pressure was abnormal but had no symptoms. Sometime after the introduction of Rauwolfia Serpentina as a blood pressure depressant she was given this drug in the form of Serpasil (Reserpine Ciba). The dosage was 0.8 mg. daily in combination with Apresoline hydrochloride (Hydralazine hydrochloride Ciba) in a dosage of 200 mg. daily. This therapy was instituted without my knowledge and only a few days after the last examination of the visual field. Within three weeks the patient returned with the complaint that the vision in the right eye had decreased. Examination showed that vision was still 20/25 in each eye, but the visual field now showed a broad, dense superior nerve-fiber bundle defect (Bjerrum scotoma) with a nasal step in the right eye and a depression of the superior nasal field in the left eye (fig. 2). There was no change in the appearance of the disc and the tonometer reading was 4/5.5 in the right eye and 4.5/5.5 in the left eye.

The Reserpine and Hydralazine hydrochloride were discontinued and the Bjerrum scotoma decreased in width and density in the right eye, while

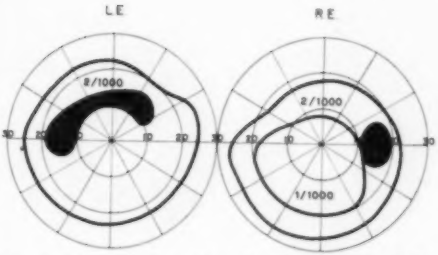

Fig. 3 (Harrington). *Case 2.* Enlargement of the blindspots and a Bjerrum scotoma in the left field.

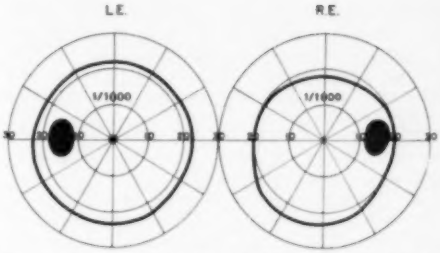

Fig. 5 (Harrington). *Case 3.* Enlargement of both blindspots and a central scotoma in the left field.

the left field also improved. Neither field, however, has returned to its previous state although there has been no demonstrable progression in the past six months.

CASE 2 (figs. 3 and 4)

Mr. K., aged 70 years, had no visual complaints but came for routine examination. Corrected vision was 20/20 in each eye. The media were clear. Both optic discs showed moderate cupping and some suspicion of atrophy, but there was a rim of normal nerve tissue around the margins. There was considerable narrowing of the retinal arterioles. The visual fields showed enlargement of both blindspots and a well-defined Bjerrum scotoma in the left field. The 1/1,000 isopter was unreliable due to poor patient response (fig. 3). Schiøtz tonometer readings were 2/5.5 and 4/7.5 in the right eye and 2.5/5.5 and 4.5/7.5 in the left eye. It was apparent that the chronic glaucoma was of long standing.

Brachial blood pressure varied between 200/100 and 215/110 mm. Hg. Diastolic pulse in the central retinal artery of the optic disc was produced by a pressure of 50 gm. with the ophthalmodynamometer.

Miotic therapy with pilocarpine was effective in controlling intraocular pressure for almost three years of observation. Tonometer readings varied from 3/5.5 to 4.5/5.5 and, except for some variation in the density of the left Bjerrum scotoma, the fields remained constant.

Because the patient manifested some evidence of kidney damage, therapy was started with Reserpine in a dosage of 0.50 mg. daily. When the patient returned in one month for his routine field and tension examination, there had been a very marked change in his visual field (fig. 4). Both visual fields now revealed broad, dense, well-established nerve-fiber bundle defects with nasal step. The right field showed a peripheral nasal breakthrough and the left a double Bjerrum scotoma. Brachial blood pressure had dropped to 130/80 mm. Hg and the diastolic pulse in the retinal artery was obtained with 25 mg. pressure. Tonometer readings were 3.5/5.5 in the right eye and 4/5.5 in the left eye and the patient had used his pilocarpine as directed. Withdrawal of the Reserpine therapy caused the blood pressure to rise again to 200/100 mm. Hg but the visual field defects remained unchanged during the next five months.

CASE 3 (figs. 5 and 6)

Mr. G., aged 68 years had noted defective vision in the left eye for about three years. Blood pressure had been elevated for some time but caused no symptoms except occasional tinnitus. Vision was 20/25 in the right eye and 20/100 in the left eye. Ophthalmoscopic examination revealed marked generalized narrowing of the retinal arteries with some areas of local constriction. There were a few superficial retinal hemorrhages and in the left macula a larger and deeper hemorrhage. Both optic discs were rather deeply cupped and there was some

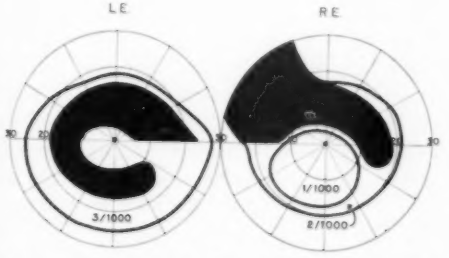

Fig. 4 (Harrington). *Case 2.* Fields one month after those shown in Figure 3.

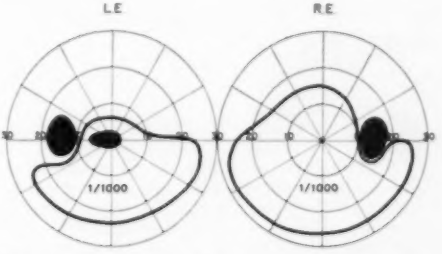

Fig. 6 (Harrington). *Case 3.* Visual fields taken a few days after those in Figure 5.

atrophy of the left optic nervehead. The visual fields showed enlargement of both blindspots and a central scotoma in the left field (fig. 5). Tonometer readings were 5/5.5 in the right eye and 4/5.5 in th left eye and these were approximated on several tests.

Brachial blood pressure was 230/110 mm. Hg with only slight variation. The diastolic pulse in the retinal artery was obtained with 65 gm. pressure. Therapy was started with an alkaloid of Rauwolfia in a dosage of 0.8 mg. per day combined with 200 mg. of hydralazine hydrochloride and the blood pressure was promptly reduced to 120/70 mm. Hg and the pressure required to produce a diastolic pulse was only 30 gm.

Within a few days the patient complained of further visual loss and, on examination, was found to have an increase in the size of his central scotoma and, in addition, a marked depression of the superior field of each eye with baring of the blindspot and a nasal step; a typical glaucoma-type field defect (fig. 6). The dosage of Reserpine was decreased to 0.25 mg. per day and the Hydralazine hydrochloride was discontinued. Blood pressure rose to 190/100 mm. Hg. The visual field loss persisted but during the following eight months it did not increase.

A second clinical observation has to do with the production of a typical glaucoma-type visual field defect in two eyes with severe papilledema. At no time during a year of observation was there an increase in intraocular pressure, but there was extreme lability of brachial blood pressure, some hypertensive retinopathy with hemorrhage and exudate and a moderate rise in cerebrospinal fluid pressure and protein content. It is believed that the visual field defects were due to circulatory insufficiency in the optic nervehead incident to violent fluctuations in blood pressure in the optic nerve arterioles combined with increased cerebrospinal fluid pressure in the optic nerve sheath, producing pressure on the arterioles in the anterior nerve.

CASE 4 (fig. 7)

Mr. W., aged 61 years, complained of visual loss in the left eye. Examination disclosed a bilateral papilledema of severe degree with retinal exudates and hemorrhages and venous stasis. Brachial blood pressure was 210/110 mm. Hg and cerebrospinal fluid pressure measured 260 mm. of water. The protein content of the spinal fluid was elevated. Vision was 20/20 in each eye and the Schiøtz tonometer readings were 4.5/5.5 in the right eye and 5.5/5.5 in the left eye.

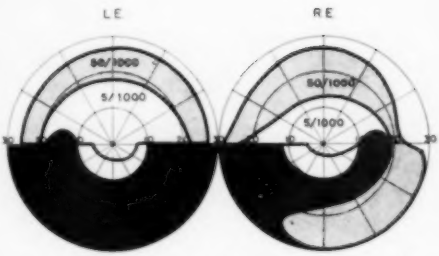

Fig. 7 (Harrington). *Case 4.* Typical inferior nerve-fiber bundle defect in the right eye and an inferior altitudinal defect in the left.

The visual fields showed a typical inferior nerve fiber bundle defect (Bjerrum scotoma) in the right eye with a broad nasal step and a break through into the peripheral field. The defect was dense and steep margined. The left field showed an inferior altitudinal defect extending from the blindspot around fixation to a steep-margined nasal step (fig. 7). During a year of observation there was little or no change in the papilledema or the visual field defect, but the blood pressure dropped as low as 130/90 and fluctuated widely. Neurologic examination, pneumoventriculograms, and the Regitine test for pheochromocytoma were all negative.

A third clinical study was made of two patients with thrombosis and insufficiency of the internal carotid artery extending into the ophthalmic artery and giving rise to visual field defects which are indistinguishable from those seen in chronic glaucoma. In each case there were subjective and objective symptoms and signs to confirm the diagnosis. In both patients there was a marked lowering of the retinal arterial blood pressure on the affected side and in one case the clinical diagnosis was confirmed by angiography.

It is believed that these two cases clearly demonstrate that arterial insufficiency, with lowered blood pressure and decreased blood flow in the arterioles of the optic nerve and the circle of Zinn-Haller, is the primary factor in the production of the typical field changes seen in chronic open-angle glaucoma. The nerve-fiber bundle defect (Bjerrum scotoma with nasal step) and the peripheral nasal depression and break through are, in short, vasogenic in origin.

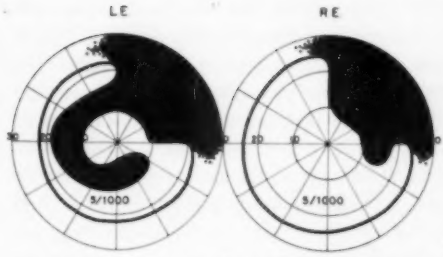

Fig. 8 (Harrington). *Case 5.* A right homonymous superior quadrantanopia and a double Bjerrum scotoma in the left.

CASE 5 (fig. 8)

Mrs. T., aged 56 years, complained of periodic attacks of blurring of vision in the left eye of about one year's duration. At first these episodes of monocular amaurosis fugax occurred at about monthly intervals and were sometimes accompanied by scintillating scotoma. There were no headaches. Initial attacks were of a few seconds' duration, but became more prolonged as they increased in frequency. Finally they were occurring several times a day and lasting for almost a minute.

When first seen this patient had just experienced a sudden visual disturbance of both eyes in association with a weakness of the right hand and arm. Examination revealed a definite motor loss in the right hand and arm, a right homonymous superior quadrantanopia, and a dense and well-established double Bjerrum scotoma in the left field connecting up with the quadrantanopic defect (fig. 8). Schiøtz tonometer readings were 6/5.5 in the right eye and 5/5.5 in the left eye. Brachial blood pressure was 120/70 mm. Hg in the right arm and 115/65 mm. Hg in the left arm. Diastolic pulse in the central retinal artery in the right eye was obtained with a pressure of 45 gm. with the Bailliart ophthalmodynamometer while in the left eye a pressure of 10 to 15 gm. was all that was required. In fact it was barely necessary to touch the eye with the footplate of the instrument to obtain a pulsation of the arteriole and collapse of the artery was produced by about 25 gm. pressure. Angiography revealed a partial occlusion of the left internal carotid artery.

CASE 6 (fig. 9)

Mr. D., aged 68 years, complained of periodic blurring of vision in the right eye, sometimes quite intense, of four years' duration. He had been aware of moderate hypertension for many years. The initial attacks of amaurosis fugax lasted one or two seconds and occurred about every two months. They increased in frequency and duration until the final attack which lasted for an hour and only partially recovered. There had been one transient episode of numbness and weakness in the left arm which lasted part of one day.

On examination visual acuity was 20/70 in the right eye and 20/20 in the left. There was narrowing and sclerosis of the retinal arterioles with some macular degeneration in the right eye. The inferior branches of the central retinal artery were narrowed, but not occluded. The left fundus showed only moderate arteriole narrowing. Tonometer readings were 6/5.5 in each eye. The visual field in the right eye showed a typical glaucomalike field defect consisting of a broad, fairly dense double Bjerrum scotoma with the superior defect breaking through into the nasal periphery and with a nasal step. There was a small central scotoma which accounted for the reduction in visual acuity. The left visual field was normal (fig. 9). The brachial blood pressure was 170/85 mm. Hg and was constant. The retinal diastolic pulse was obtained in the right eye with a pressure of less than 20 gm. while it required 50 to 60 gm. to elicit the pulse in the left eye. A number of readings were consistent in showing this difference in the two eyes.

The patient was given treatment with dicumarol and heparin and there was an improvement in vision to 20/30 and a regression of the central scotoma in the left field. The nerve-fiber bundle defect remained unchanged. Dicumarol therapy was discontinued, but heparin in small doses was continued and there have been no further attacks of amaurosis fugax.

DISCUSSION

For many years arguments as to the "neurogenic" or "vasogenic" origin of the visual field defects of chronic glaucoma have been debated in the literature, nor is the conflict yet resolved.

Controversy over the merits of ophthalmodynamometry has raged for 45 years and is still going on. This clinical method of measuring arterial pressure in the eye, or in the vessels immediately behind it, has been used by European ophthalmologists with varying success for a long time. Only very recently have American ophthalmologists

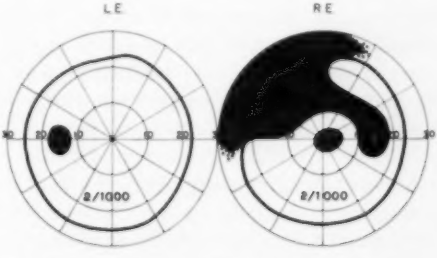

Fig. 9 (Harrington). *Case 6.* A typical glaucomalike defect in the right eye; the left field normal.

and neurosurgeons rediscovered its value, especially for the study of cerebral circulatory disorders.

In just a few years there has accumulated a vast literature on these subjects. A pertinent few of these articles will be cited in support of the clinical observations and the theories advanced in this paper, namely that the visual field defects of chronic glaucoma are vasogenic in origin and that they are the result of circulatory insufficiency in the anterior portion of the optic nerve. This circulatory insufficiency results from an imbalance between intraocular pressure and arterial and capillary pressure in the optic nerve. This imbalance may be produced either by an abnormally high intraocular pressure or an abnormally low arterial pressure or both.

In 1942 Reese and McGavic[1] assumed that the field changes in glaucoma had a vascular basis and that the relation between intraocular pressure and retinal blood pressure was important in the determination of field loss. They measured the percentage of visual field retained in 132 cases of glaucoma and correlated it with the ratio between systolic and diastolic blood pressure and intraocular pressure. They expressed this ratio as a coefficient and established a normal. For example, if the systolic blood pressure was 125 mm. Hg and intraocular pressure was 25 mm. Hg the systolic coefficient would be 5.0. For each of the 132 patients the percentage of visual field retained and the systolic and the diastolic coefficient were obtained. From these figures it was deduced that a systolic coefficient of 5.75 to 6.0 or higher and a diastolic coefficient of 3.25 to 3.50 might be considered normal. Those patients with coefficients in the higher ranges tended to lose visual field more slowly than those whose coefficients were in the lower range.

Lauber[2] had previously suggested that the field changes in glaucoma are due to an altered relation between high intraocular pressure and normal retinal vascular pressure and had cited J. Gallois as stating that the field of vision suffers when the blood pressure of the patient with glaucoma is lowered.

McLean[3] confirmed the findings of Reese and McGavic[1] that there is a relation between the level of systemic blood pressure and tolerable intraocular pressure and further remarked that he had seen a patient lose field at the same tension level on which he had previously maintained it when his physician succeeded in drastically lowering his systemic blood pressure.

McGuire[4] postulated that the most reasonable explanation for the progressive field changes in chronic simple glaucoma is arteriosclerotic changes in the nutrient vessels of the optic nerve. These changes may involve slowing of the blood stream, narrowing of the lumen of the vessels and formation of atheromatous plaques and mural thrombi. McGuire felt that treatment with a vasodilator with anticoagulant properties might be effective in such cases and reported nine such patients with chronic glaucoma and progressive visual field loss in which there was remarkable restoration of the visual field, often to normal, following therapy with 4-hydroxycoumarin (dicumarol).

Nordmann[5] reports that even in advanced glaucoma with marked visual field loss the injection of d-amphetamine (maxiton or dexidrine) produced dramatic and remarkable improvement in the visual fields. This might well be due to the blood pressure-elevating effect of the drug.

Gafner and Goldmann[6] report a diminished sensitivity in the area of the field between 10 and 25 degrees (Bjerrum region) in early glaucoma simplex cases. The same phenomenon was caused by pressure on the globe sufficient to produce increased intraocular pressure in normal eyes. It could not be produced in normal persons by decreased oxygen intake or by compression of the neck vessels. From the fact that the pressure necessary to effect these phenomena is correlated to the pressure in the ophthalmic artery it is concluded that the Bjerrum scotoma of chronic glaucoma is due to disturbance in blood circulation in the optic nerve fibers. The authors then demonstrate, with

an electric model, equivalent to the schematic nutrition of the posterior globe and the anterior optic nerve through the central retinal artery, the short posterior ciliary arteries, and the central artery of the optic nerve, that an increase in intraocular pressure causes a diminution in the rate of blood flow in the lamina cribrosa. The same changes can be effected by a diminution of pressure in the arteries supplying this region without any elevation of intraocular pressure. They point out the origin of these arterioles from the ophthalmic artery. The authors report a case of Addison's disease with low systemic blood pressure and rapid visual field lose and they cite Bailliart as stating that in cases with high pressure in the ophthalmic artery damage to the visual field is delayed.

Niedermeier[7] believes that trophic vascular changes of age can be demonstrated in the vascular supply of the lamina cribrosa and that these changes cause optic nerve excavation. His clinical investigations support Goldmann's thesis that these circulatory disturbances are in the region of Haller's circle. In 11 cases of early glaucoma, without optic atrophy and field loss, intravenous injection of Evans blue showed a change in permeability in the region of the circle of Haller when the intraocular pressure was 30 mm. Hg.

Anatomic evidence that the site of the lesion producing the glaucoma field defect is in the vascular supply of the anterior optic nerve may be deduced from the brilliant demonstrations of François and Neetens[8, 9] which are now well known and accepted.

By the method of Neoprene latex injections of the vascular system of the globe and optic nerve and later by microarteriography they were able to show that the central retinal artery does not supply the optic nerve, but only the retina; that the ophthalmic artery gives off, very early in its course, a central optic nerve artery which forms the axial nutritional system of the optic nerve; that there is capillary anastomosis between this "central artery of the optic nerve" and the circle of Zinn-Haller to supply the optic papilla and that capillaries from anastomoses between the extraorbital cerebral vessels help to supply the optic nerve through the pial sheath vessels. Thus the peripheral vascular supply is through a pial network while the axial supply is through the central artery of the optic nerve.

Redslob,[10, 11] in two papers, discusses the problem of optic atrophy in glaucoma and the mechanism of its production. In a comprehensive histopathologic study of 60 eyes affected with primary glaucoma he found the retinal elements well preserved in most cases, but the optic disc cupped and atrophic in 95 percent of cases. Alteration of the circulation was a constant finding in glaucoma due to sclerosis of the arteries and arterioles and to stasis in the veins and capillaries. Capillary sclerosis follows and this is the principal cause of the descending atrophy of the optic nerve in glaucoma.

DuBois-Poulsen[12, 13] experimentally produced a Bjerrum scotoma by injecting five percent formalin into a cysticercus cyst on the outer aspect of the optic nerve immediately behind the globe. The nasal step of Rønne was produced in a normal human eye by dazzling the central portion of the retina. He concludes that neither field defect is confined to glaucoma or necessarily related to increased intraocular pressure, but that the nasal step is the result of unequal fall in sensation in the upper and lower retinal quadrants and that the lesion producing the Bjerrum scotoma is in a well-separated nerve-fiber bundle posterior to the eye, either near the globe from a disturbance in the Zinn-Haller arterial circle or farther back in the optic nerve.

The literature on carotid artery thrombosis and that on the clinical uses of ophthalmodynamometry are growing rapidly and much of it is interrelated. Numerous authors comment on the ocular signs of carotid artery thrombosis.

Walsh[14] states that thrombosis of the internal carotid artery may account for blindness of the homolateral eye and attributes it

to an extension of the thrombosis to the ophthalmic and thence to the central retinal artery. He also mentions the transient visual loss which precedes the development of hemiplegia.

Rucker[15] comments on the occurrence of transient and permanent monocular visual loss in thrombosis of the internal carotid artery and on the diagnostic value of ophthalmodynamometry in recording marked differences in diastolic retinal blood pressure in the two eyes.

Most authors now agree that the determination of absolute values for the systolic and diastolic pressure in the retinal arteries is not feasible by the method of ophthalmodynamometry. The majority, however, believe that the method of Bailliart[16, 17] has considerable merit as a diagnostic tool when wide differences in arterial pressure are recorded in the two eyes (Streiff,[18] Goldmann[19]) and it seems generally agreed (Heyman,[20] Van Allen,[21] and Thomas[22]) that carotid artery insufficiency or thrombosis produces marked lowering of arterial blood pressure in the ophthalmic artery and its branches. This might well extend into the central retinal artery or into the central optic nerve artery, producing an imbalance between intraocular pressure and arterial pressure in the anterior portion of the optic nerve.

Summary

Three different clinical observations (in six cases) are presented, each of which seems to contribute further evidence to support the theory that arterial insufficiency and decreased blood flow in the anterior portions of the optic nerve are the main factors in the production of visual field loss in glaucoma.

All six cases demonstrated the advanced visual field defects typical of chronic glaucoma. The common factor in each case was an imbalance in the normal ratio of intraocular pressure to arterial pressure in the arteries supplying the optic nerve. A few of the pertinent articles in the literature which have advanced or supported this theory have been cited.

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NEMATODE ENDOPHTHALMITIS: TOXOCARA CANIS

Report of one case

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In 1950 Wilder[5] reported a series of 46 eyes, of which 24 were found to contain nematode larvae or fragments thereof. Chitwood considered these to be third-stage hookworm larvae. All of the 24 confirmed cases of parasitic infestation occurred in children of preschool or early school age. The single additional case herein reported is, in a large measure, the direct result of the stimulus provided by Wilder's contribution.

The syndrome of visceral larva migrans is believed by Dent,[3] et al., to be caused only by the dog and cat ascarids of the genus Toxocara. The natural hosts of these worms are dogs (T. canis), and cats (T. cati), and the infection is acquired by the ingestion of eggs from contaminated soil. An examination of dooryard soil in Georgia and Louisiana revealed a considerably higher contamination from T. canis than from T. cati. It has been proposed that this may be attributable to the general cleanliness of cats as compared to dogs. A survey of 1,465 dogs in Indiana and adjoining states revealed the presence of T. canis in 21 percent. Among this group the sex distribution predominantly favored males, and the incidence was higher in both male and female pups than in the adult animals.

The larvae of T. canis do not complete their life cycle within the human host but are capable of invading human viscera, where they may survive for many months. Structurally they resemble Ascaris lumbricoides, and in their canine hosts follow a similar life cycle to that of A. lumbricoides in man.

According to Nichols,[4] the larvae shrink in the preparation of tissue specimens to about one fifth of their original length. He found the maximum diameter to be 18 to 21 microns. Dent,[3] et al., reported measurements of 360 to 440 microns in length and 18 to 22 microns in diameter in their series. They state that the larva has roughly two portions; a clear esophageal region which makes up less than one third of the total length, and a more dense intestinal part packed with refractile globules, and ending circa 60 microns anterior to the tip of the tail. They are cylindric, elongated organisms with the body having almost parallel lateral margins as seen in the optical plane. The anterior quarter of the body tapers equally to a three-lipped, subterminal, dorsally inclined mouth. The larva of T. canis can be accurately identified in stained sections by several morphologic characteristics not shared by other nematodes; that is, in transverse sections through most levels of the larva, single lateral alae are formed by sharp foldings of the cuticle in the lateral line. The alae are more pronounced at the level of the posterior esophagus, and at all intestinal levels. The intestine has no lumen,

and consists of seven elongated cells arranged in linear fashion. It can be seen accurately only in transverse sections.[4] In longitudinal sections stained with Giemsa and hematoxylin, minute granules associated with the cytoplasm of intestinal cells are often seen. Median sagittal section of the buccal apparatus show the typical ventral cuticular spinelike structure of T. canis, and are morphologically diagnostic.

After the ova are ingested they hatch in the stomach and intestine, migrate through the walls of these organs, and are disseminated via the blood, lymphatics and tissue spaces.[3]

Clinical survey

In the human, T. canis infestation occurs predominantly in children of preschool or early school age. There is often a history of dirt-eating (geophagia), or close contact with dogs. Fever, general debility, and pulmonary and hepatic involvement are frequently present. Eosinophilia is typical, and in some cases exceeds 50 percent. This finding, together with general symptoms, has been often attributed to other intestinal helminths. Infections from T. canis are probably more prevalent than supposed, and it seems reasonable to assume that the severity of clinical symptoms and the degree of eosinophilia are roughly proportional to the number of ova ingested.[1]

The possibility of ocular T. canis infestation should be suspected from the clinical history and physical findings. The diagnosis is confirmed only by serial sections taken from tissues harboring the larva or fragments thereof. Due to the failure of the larva to complete its life cycle in the human, stool examinations are noncontributory, which is in contrast to the findings in many cases of A. lumbricoides. Skin tests have been inconclusive in nematodiasis resulting from T. canis.[1]

Differential diagnosis

Infection with other intestinal helminths —especially A. lumbricoides—pneumonia, asthma, whooping cough, Loeffler's syndrome, and tropical eosinophilia are general diseases to be excluded.[1] From the ophthalmic viewpoint, retinoblastoma, endophthalmitis, and the general groups of severe exudative and hemorrhagic retinopathies may present a similar clinical picture. In particular, any child showing the clinical signs of pseudoglioma should have an eosinophil count.

General course and therapy

A chronic course lasting from one to two years is common. The prognosis for life is favorable, and is explained by the minute size of the lesions which ultimately heal by fibrosis. No specific therapy has been discovered, and treatment is therefore palliative.[1, 3]

In laboratory animals a high percentage of the larvae persist and retain infectivity for two or more years. In organs other than the brain, they become encapsulated.[1]

General pathology

Dent,[3] et al., report microscopic findings of biopsy and necropsy material from the liver, lung, brain and spinal cord. These tissues reveal focal granulomas with and without fibrinoid necrosis. Eosinophilic abscesses were characteristic, and in serial sections T. canis larvae were identified. Those granulomas containing numerous foreign body giant cells usually revealed no larvae, and none were present in the multinucleated giant cells. In the liver specimens, the entire parasite was occasionally surrounded by granular fibrinoid material, and degenerating larvae by foreign body giant cells and epithelioid cells. Parasites and their fragments stained dark red in the periodic acid-Schiff preparations, and periodic acid-Schiff positive débris was present in the fibrinoid material of the granulomas. All of the tissues were fixed in 10-percent formalin. Routine hematoxylin eosin, Giemsa, and periodic acid-Schiff stains were used.

In Wilder's[5] cases no nematodes were present in the routine sections. Only in se-

rial sections could the larva or its fragments be demonstrated, and characteristic lesions —in which T. Canis larvae were later identified[1]—were present in the choroid, the retina, and the vitreous. The anterior segments were not remarkable. Cataractous changes were common.

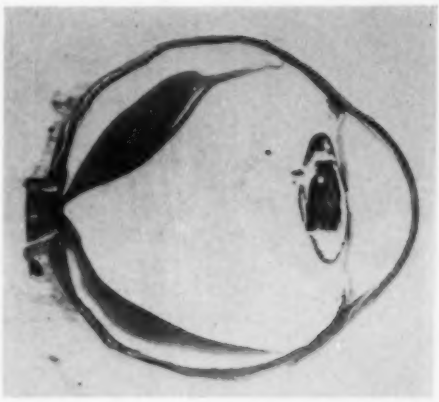

Fig. 1 (Irvine and Irvine). Whole mount. Retinal detachment. Subretinal serous exudate. Anterior segment normal.

Case report

The left eye of K. R., a four and a half-year-old Caucasian boy, a patient of Dr. Edward H. Crane, Jr., was received at the Estelle Doheny Eye Foundation in November, 1955.

History. The patient was born and had lived in Indiana until the age of three years. In October, 1955, his mother noted that his left eye intermittently "turned out." A medical survey revealed a normal healthy boy without any significant family or past history. A system review was noncontributory. The red blood count was 4,230,000; hemoglobin 79 percent; white blood cells 5,900, with six percent eosinophils. The urine analysis was normal.

Ophthalmologic findings. Vision: O.D., 20/20; O.S., 20/70 (illiterate chart). The right eye was normal.

The left eye was normal in size, not inflamed, and the digital tension not elevated. The cornea was clear. Nodular pigment deposits were seen on the iris and anterior lens capsule. The aqueous was clear. The lens and vitreous were reported to be clear. A retinal detachment was seen inferiorly with a plus 12 to 15 lens. The apex of the detachment appeared to be solid, and extended almost to the macula. The eye transilluminated poorly below. The P^{32} uptake was positive, and a Papanicolaou stain of aspirated aqueous was positive for malignant cells. Clinical diagnosis: Retinoblastoma.

Pathology (588-55)

Gross description. The specimen is a left eyeball fixed in 10-percent formalin. It is of normal contour and measures: anteroposterior, 22 mm.; horizontal, 22 mm.; and vertical, 22 mm. The sclera is white. The optic nerve is six-mm. long. Transillumination is good. The cornea is transparent and the epithelium intact.

The eye was opened vertically, the larger calotte was taken temporally. The anterior chamber is somewhat shallow. A flat, yellow lens is in place. A clear coagulum fills the vitreous cavity. Inferiorly at the ora serrata, a white, fingerlike projection extends into the vitreous, and a firm gray, translucent subretinal coagulum is present from the ora to the topic nerve. There is no evidence of intraocular tumor.

Microscopic description. (Sections 14 microns thick and cut meridionally. Hematoxylin-eosin and periodic acid-Schiff stains.) The retina is detached from the ora serrata to the disc by a serous exudate (fig. 1). Of particular interest is the presence of an eosinophilic abscess at the ora serrata and pars plana inferiorly (fig. 2). A central area of necrosis is seen in most sections, and when examined serially, 10 sections demonstrated the presence of a nematode larva (figs. 3, 4, 5, and 6) in the region of necrosis. The parasite is fragmentary in some slides (figs. 7 and 8), while in others, the characteristic morphology of the T. canis larva can be discerned (fig. 6).

In 20 slides a well-marked polymorphonuclear reaction is seen in the necrotic area. These cells show varying degrees of disintegration. A surrounding zone consisting chiefly of plasma cells—some of which are multinucleated—and lymphocytes is seen, and in this region, in some sections, ill-defined epithelioid cells effect a palisading arrangement. Eosinophils are conspicuous in and adjacent to the granuloma (fig. 7).

The inflammatory reaction extends in

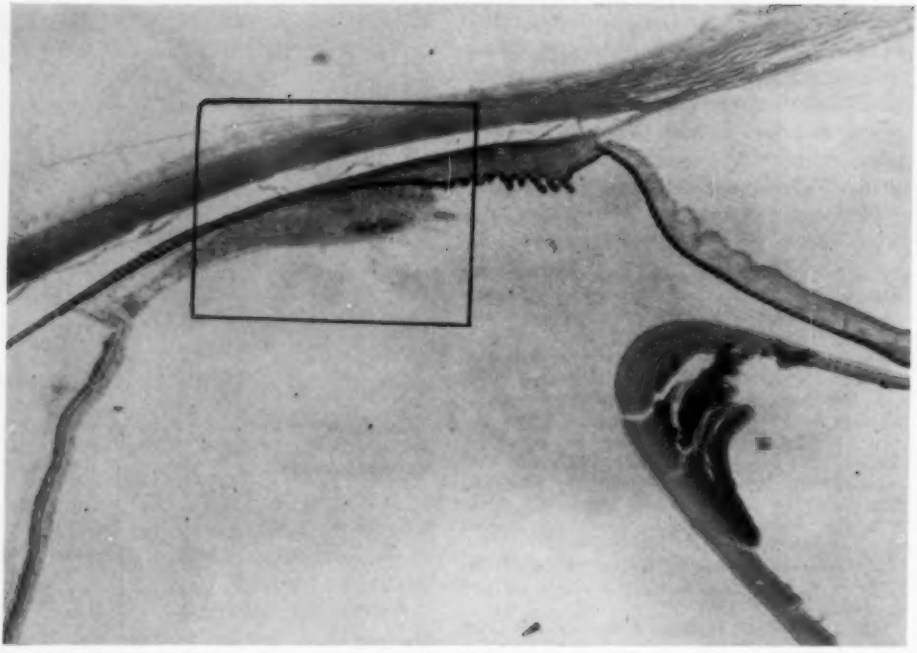

Fig. 2 (Irvine and Irvine). Low power of eosinophilic abscess involving ora serrata and pars plana.

minor degree to the circumlental region, the vitreous, and on the internal limiting membrane of the retina. Giant cells are rare. Early fibrosis is present at the edge of the abscess.

It is of special interest that no inflammatory foci involve the choroid. Posterior to the abscess the retina is free from inflammation except for occasional perivascular lymphocytes.

The optic nerve is normal.

The corneal epithelium and stroma are not involved. The corneal endothelium appears normal, and no inflammatory cells are adherent to it. Isolated clumps of pigment are present on the anterior surface of each iris leaf. The iris stroma contains numerous chronic inflammatory cells, the majority of which are plasma cells and lymphocytes. Occasional eosinophils are also seen in many

Fig. 3 (Irvine and Irvine). Low power. Arrow points to nematode larva in center of necrotic abscess.

Fig. 4 (Irvine and Irvine). Higher power of Figure 3. Larva surrounded by inflammatory débris, epithelioid cells, polymorphonuclear leukocytes, and eosinophils.

sections. The chamber angle is similarly involved, but to a comparatively minimal degree. The anterior lens capsule is speckled with occasional pigment deposits and occasional chronic inflammatory cells are seen. The lens is not remarkable.

Pathologic diagnosis. Nematode endophthalmitis (Toxocara canis).*

Discussion

The usual activity and distribution of T. canis in the human host as reviewed in this report[1-3] add further impetus to the natural speculation aroused by the apparent ocular selectivity of the parasite in our case. The clinical absence of other organic involvement, however, is probably misleading. If the degree of eosinophilia is an index of the number of ova ingested,[3] it would appear that minimal infestation occurred in this instance, as only six percent eosinophils were reported in the blood smear. But while this possibility cannot be disregarded, it seems more plausible to assume the presence of clinically innocuous minute granulomas in other organs, particularly the liver and the lungs.

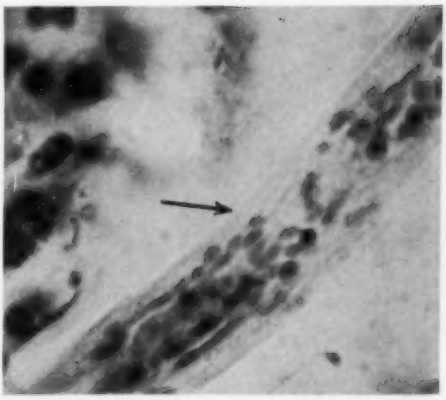

Fig. 5 (Irvine and Irvine). Higher power of larva and inflammatory reaction. Arrow indicates lateral hyaline capsule.

We are forced to conclude—in the absence of choroidal involvement—that the infestation in our case occurred via the end-arterioles of the retinal vasculature. Wilder[5] postulated that the larvae in her series were

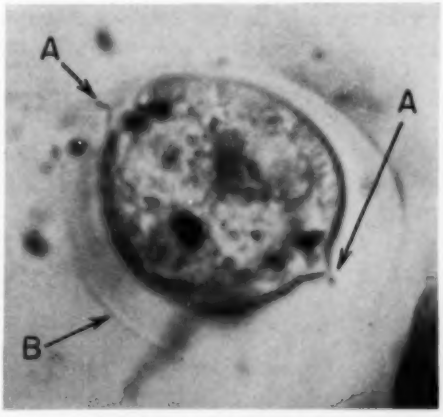

Fig. 6 (Irvine and Irvine). (Oil immersion.) Transverse section of larva—intestinal level. Hyaline capsule (B), and characteristic spinelike alae (A).

* Dr. R. L. Nichols reported, "Toxocara canis is evident and recognizable in any single transverse section."[6]

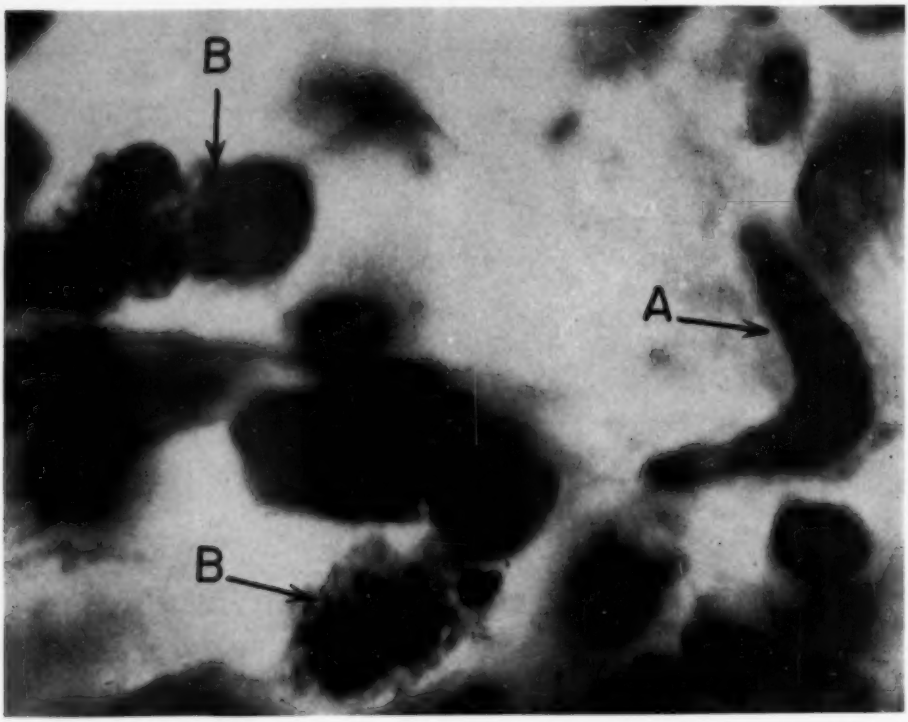

Fig. 7 (Irvine and Irvine). (Oil immersion.) Hyaline capsular fragment (A). Note large eosinophils (B).

transmitted by the ciliary vessels to the choroid. She demonstrated secondary invasion of the retina and vitreous.

The lesion in the case herein described is estimated to be 0.44 mm. in size, while the diameter of the larva measured 18 microns at midgut and 11 microns at the esophageal level. The importance of examining serial sections in any suspected case of nematode infestation is therefore obvious. While one

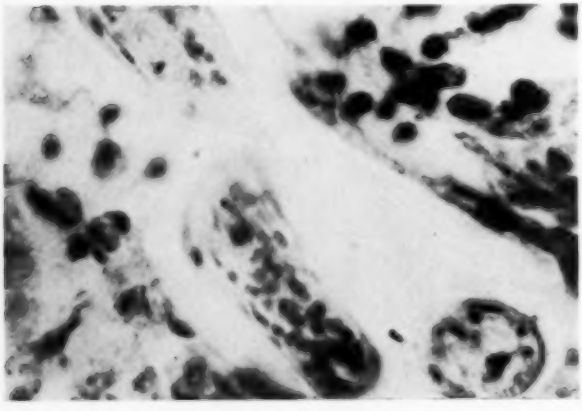

Fig. 8 (Irvine and Irvine). (Oil immersion.) Longitudinal fragments of larva and transverse section in lower right hand corner showing spiny process and part of surrounding capsule (see figure 6).

larva was noted in the routine sections of this case, its usual absence on routine sectioning is emphasized by the fact that only in serial sections were larvae found in Wilder's[5] series; indeed in one case, examination of more than 3,000 sections revealed but one nematode.

Considering the very small size of the pathologic lesion, it is interesting that the P^{32} uptake was positive, and one can only conjecture as to the appearance of the "malignant cells" reported on the Papanicolaou stain of aspirated aqueous.

The ophthalmic and public health import of Wilder's contribution—to which this case may be added—cannot be emphasized too greatly. The identification of T. canis in her series, and in this single case, adds yet another nematode to the list of those known to invade the eye. It is hoped that this report will serve to increase the awareness of ophthalmologists in this country to the possibility of intraocular T. canis infestation. And while this nematode has been added to the etiologic armamentarium of ophthalmology, its household counterpart, T. cati, is awaiting recognition.

Summary

1. A case of Toxocara canis infestation involving the left eye of a four and a half-year-old boy is reported.

2. Pertinent data in the literature are reviewed.

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Acknowledgment

Appreciation is expressed to Mrs. Helenor Wilder Foerster for examining sections of this nematode and advising means of its proper identification; to the parisitologists—particularly Dr. R. L. Nichols and Dr. P. C. Beaver—who established its identity; to Dr. John Kessel of the University of California Medical Center who took measurements of the larva; to the staff of the Estelle Doheny Eye Foundation, especially Mrs. Jean Mannagh, for her technical assistance; Mr. Zolton Yuhasz for the photography; and Miss Mary Mellott for assistance with the manuscript.

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HISTOLOGIC ASPECT OF CORNEAL CHANGES*

Due to hereditary, metabolic, and cutaneous affections

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Only recently has attention been drawn to corneal changes which become manifest in the course of systemic diseases of hereditary origin. In the past the corneal changes were often considered not as a local manifestation of the general affection but as a complication of lid or conjunctival changes. Sometimes the corneal affection may only be revealed after close examination with the slitlamp. Very little is known about the pathologic anatomy of the corneal changes because only a few cases have been examined histologically.

Since reports of A. Franceschetti, D. Klein, S. Forni, and J. Babel on heredo-

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familial degeneration of the cornea (XVI International Congress of Ophthalmology, London, 1950) and that of A. Franceschetti, D. Klein, and J. Babel on the ocular manifestations of primary disturbances in lipid metabolism (XIX International Congress of Oto-Neuro-Ophthalmology, São Paulo, 1954) we have had the opportunity to examine a series of new cases at the Clinic of Ophthalmology in Geneva, both from the clinical and from the histologic point of view. This fact would seem to justify the publication at this time of a general review of the histology of corneal changes related to metabolic and cutaneous diseases of hereditary origin.

I. Metabolic diseases

A. Pfaundler-Hurler's disease

In this polydystrophic disease, also known under the name of gargoylism, it is possible to observe numerous ocular changes of a dysmetabolic, dysmorphic, and malformative type (Moro, 1957). Among these changes the most frequent is corneal opacity (75 percent), which is characterized by its bilaterality, by its very early and sometimes even congenital appearance, and by its stationary character.

Many investigations demonstrate that gargoylism may be considered as a metabolic disturbance either of one mucopolysaccharide or possibly of one mucoprotein with accessory thesaurismosis of a lipid substance. This metabolic disturbance, possibly based on an enzymatic deficiency, could easily explain the derangement of growth and the skeletal deformities found in this disease, for the mucopolysaccharides play an important role in the development and the functions of the connective tissue.

In the literature it is possible to find 21 cases in which the cornea has been examined histologically (table 1). Among the publications quoted, Rochat (1942) and Zeeman (1942) gave a histologic description of two eyes from the same case. The cornea was clinically and histologically normal in a single case (Sartori and Baruffaldi, 1953).

We have had the opportunity to perform corneal biopsies in three familial cases of slightly atypical gargoylism. The clinical data on these cases have been previously published by F. Bamatter (1956, obs. 6-8).

The general condition of the patient was very similar in the three cases. The changes, which started at about the age of three or four years, were manifested by a slow mental regression, the appearance of an incoordinated, pithecoid walk, and by a change in the facial expression which became more or less dull and expressionless.

Case reports

The two sisters and brother suffering from this disease showed such slight corneal changes that they were definitely visible only with the slitlamp.

Case 1 (Clin. 12389/1956, St. . . . Jean-Pierre, born, 1946)

Biomicroscopic appearance. Bilateral diffuse dustlike superficial opacities were present, more marked on the nasal side and limited to the pupillary region by a festooned whitish line with garlanded borders. In the deep layers on both sides there are some fine punctuate opacities of the cornea; the posterior surface of the cornea has a hammered-silver appearance (fig. 1).

Histologic examination. Regularity of the epithelium, swelling, vacuolization, and formation of pseudocysts, especially in the basal layers are seen.

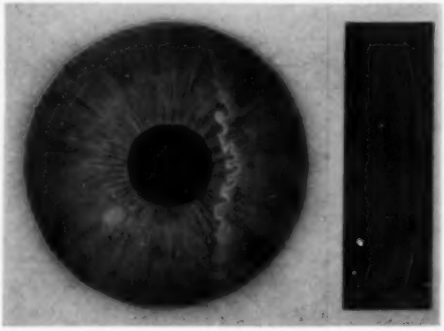

Fig. 1 (Forgács and Franceschetti). Gargoylism. Slitlamp view of the cornea. Superficial dustlike opacity with festooned line on the nasal side. Two larger spots in the inferior temporal quadrant. (Personal obs. Case 1, R.E.)

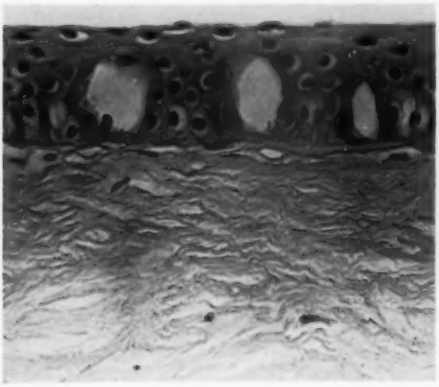

Fig. 2 (Forgács and Franceschetti). Gargoylism. Corneal biopsy. Cystic formations in the basal layers of the epithelium. (Case 1, hematoxylin-eosin, ×353.)

Bowman's membrane is almost completely absent; only a few fragments remain. In its place a fibrillary connective layer is found with a slight increase in the number of cells. These cells are not vacuolated, nor are they more voluminous than the other cells of the stroma (fig. 2).

With PAS staining neither granulations nor deposits are found in the epithelium.

Case 2 (Clin. 12390/1956, St. . . . Sylvania, born, 1948; sister of Case 1)

Biomicroscopic appearance. Slight diffuse dustlike opacities, localized in the superficial layers of the cornea, are seen on both sides.

Histologic examination. The appearance differs only slightly from that of Case 1. The cystic formations in the basal layer of the epithelium are a little less marked. The basal membrane of the epithelium is present but is very faintly stained. Some rare intracellular granulations in the epithelium are colored by PAS. The stroma presents a normal aspect, no vessels being present (fig. 3).

Case 3 (Clin. 12391/1956, St. . . . Jacqueline, born, 1949; sister of Cases 1 and 2)

Biomicroscopic appearance. A diffuse dustlike opacity is seen on both sides. The opacities are round and in the form of a garland in the inferior nasal quadrant of the right eye. In the left eye there are some larger opacities in the inferior nasal quadrant and a larger garlanded line in the inferior half. All these opacities lie at the level of Bowman's membrane (fig. 4).

Histologic examination. The changes are similar to those found in Cases 1 and 2. In a few places Bowman's membrane is preserved, but in most places it is replaced by a fibrillary layer (fig. 5).

Our histologic observations of the epithelial alterations are very similar to those which have been described by other authors. The principal changes are swelling and vacuolization of cells in the basal layer, as well as the formation of pseudocysts. These alterations cannot, however, be considered as specific. We have been able to confirm that Bowman's membrane is partially absent, frayed in places, and replaced by fibrillary connective tissue containing spindle-shaped cells. In agreement with Moro, we have found some rare granulations in the epithelial cells colored with McManus (PAS) which may be considered as a product of cellular metabolism.

We have not found spumous cells described by several authors and considered as specific formations in this disease. Neither have we found lesions in the stroma. Perhaps these differences may be explained by the discrete corneal changes in our somewhat atypical cases.

Fig. 3 (Forgács and Franceschetti). Gargoylism. Corneal biopsy. Two cells containing small colored granules are seen in the middle layer of the epithelium. (Case 2, PAS.)

TABLE 1

HISTOLOGIC CHANGES OF THE CORNEA IN CASES OF GARGOYLISM PUBLISHED IN THE LITERATURE

Author	Cornea				
	Clinical Appearance	Histologic Appearance			
		Epithelium	Bowman's membrane	Stroma	Endothelium Descemet's Membrane
1 Kressler and Aegerter (1938)	Diffuse opacities beginning at the periphery (visible with the naked eye)	—	—	Dissociated lamellae	—
2 Berliner (1939)	Dense milklike opacity. Yellowish-white deposits in the middle and deep layers	—	Absent in places and replaced by globular fusiform cells	Granular substance in the interlamellar spaces. (Lipid granules)	Intracellular granules
3a Rochat (1942) (one eye case Waardenburg 1940)	Diffuse opacities especially in the anterior layers. Filamentary and punctate spots, like snowflakes	—	Absent in places, otherwise thinned or split into two lamellae. At the level of destruction abound cells with protoplasm containing slightly brilliant granules isolated or confluent (like masses of snowflakes)	Fine granulations in the protoplasm of the corneal cells in places	—
3b Zeeman (1942) (Other eye case Waardenburg 1940)		Fine granulation of the protoplasm in the basal cell layer			—
4 Weidenmüller (1944)	—	—	—	Lipoid disturbances in the corneal cells	—
5 Hogan and Cordes (1944) Case 1	Uniform distribution of gray punctate spots throughout the corneal stroma	—	Thinned in places with numerous dehiscences filled with large polygonal or round cells, with finely granulated cytoplasm	Swollen corneal cells containing a finely granulated substance	—
6 Case 2	The same spots but more pronounced in the deeper layers	—			—
7 Case 3	Cornea opaque	—			—
8 Strauss (1948)	Diffuse punctate opacities of the cornea	—	A group of swollen elongated cells, parallel with the surface, with eosinophilic cytoplasm	—	—
9 Lindsay and coll. (1948) Case 3	Corneal opacity. Numerous small, refractile bodies in the deeper layers	Thickened epithelium	Replaced by swollen, finely granulated connective tissue cells. (Scarlet-red negative)	Hypertrophic corneal cells, filled with a granular substance, enlarging the interlamellar spaces	Vacuolization of the cytoplasm of endothelial cells
10 Case 4	Diffuse opacity				
11 Case 7	Corneal opacity				
12 Wagner (1949)	Complete opacity of the corneal stroma	—	Absent in places, and replaced by cells with spumous cytoplasm, filled with lipid granules	The corneal cells contain some lipid granules	—
13 Wexler (1951)	Diffuse opacity of the stroma	—	Interrupted in places, dissociated in others. Infiltration of large spumous granules under the epithelium	The periphery of the enlarged interlamellar spaces is occupied by a granulous substance, (slightly colored by Eosin, strongly colored with Mallory). At the edge of the round or fusiform cellular spaces, some disintergrating	—
14 François and Rabaey (1952)	Epithelium rough. Diffuse more or less confluent punctate opacities of the stroma (appearance of an emulsion)	Irregular disposition of the basal cells. Many vacuolated	Absent in many places and replaced by swollen cells containing a granular mass	Enlarged interlamellar spaces containing a granulous coagulated mass (intracellular?)	—
15 Henderson and coll. (1952)	Diffuse opacity	—	Small deposits of foam cells.		—
16 Sartori and Baruffaldi (1953)	Normal		Normal		

TABLE I—*Continued*

Author	Cornea				
	Clinical Appearance	Histologic Appearance			
		Epithelium	Bowman's membrane	Stroma	Endothelium Descemet's Membrane
17 Newell and Koistinen (1955) Case 1	Cornea cloudy	—	Cracked by large swollen cells, some without a nucleus, which are found mostly at the limbus. The cytoplasm of these cells is rose-colored with anilin and fuchsin	Enlargement of the interlamellar spaces containing a substance colored pink with anilin, blue-orange G-fuchsin. Corneal cells swollen and filled with a reddish staining substance	Endothelial cells vacuolized
18 Case 2 (both eyes)	Diffuse opacity Disc-shaped opacities especially at the center of the stroma (slit-lamp)	—			
19 Case 3 (brother of Case 2, both eyes)	Disc-shaped opacities of the stroma (only visible at the slitlamp)	—			
20 Moro (1957)	Uniform grayish milky appearance of the parenchyma; sparing the anterior layers. In this cloudiness, small regular spots are distinguishable	Basal cells more voluminous in places. Fine PAS+ granulations in the cytoplasm. Often of irregular arrangement. In places intraepithelial pseudocyst formation containing PAS+ granules.	Cavities of different sizes forming a kind of lattice, in places occupied by histiocyte cells with foamy cytoplasm, containing PAS+ granulations	Transformation of the fixed elements into histiocyte type cells with foamy cytoplasm and PAS+ granulations. Swelling of the lamellae with changes in their orientation	—
21 Anderson, Margolis and Lynn (1958)	—	—	Foamy histiocytes between Bowman's membrane and the epithelium	The laminae of the cornea are slightly separated by a vacuolar cytoplasmic swelling of the stroma cells	—

B. Diseases of the lipid metabolism

In Hand-Schüller-Christian's disease, lipid infiltration of the cornea is rarely observed. Histologic examination of the cornea has been performed in only a few cases (Jaensch, 1934; Grancini, 1940; van der Hoeve, 1948) and these showed the presence of numerous spumous cells containing birefringent lipids and in addition evidence of a chronic inflammatory reaction.

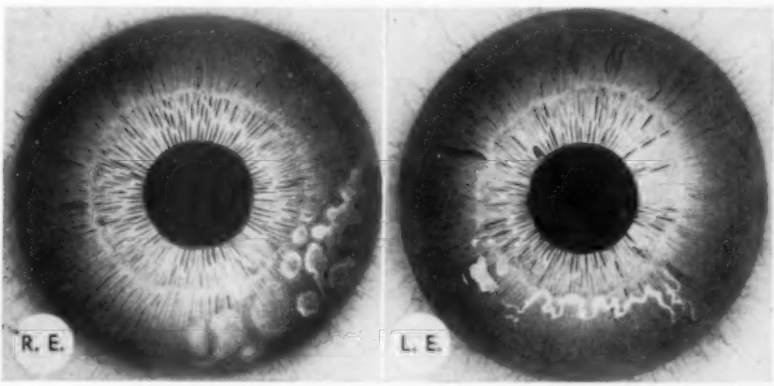

Fig. 4 (Forgács and Franceschetti). Gargoylism. Slitlamp view of the cornea. There is a diffuse dust-like superficial opacity in both eyes; there are also round opacities in the form of a garland, especially in the nasal and inferior part. (Case 3, R.E. and L.E.)

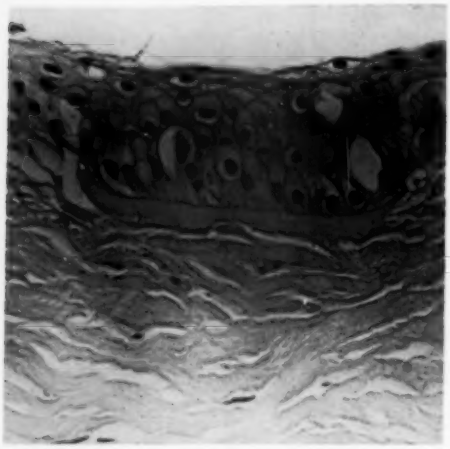

Fig. 5 (Forgács and Franceschetti). Gargoylism. Microscopic appearance of the corneal biopsy. Numerous cystic formations in the epithelium. Teasing out of Bowman's membrane and its replacement by connective tissue is seen on both sides of the figure. (Case 3, hematoxylin-eosin, ×353.)

The dermo-chondro-corneal dystrophy described by François (1949, 1952) is characterized by enchondral ossification disorders, xanthomatoid nodules of the skin, and corneal dystrophy which shows, histologically, the presence of large partly vacuolated histiocytes in the region of Bowman's membrane.

C. Cystinic diathesis

It is well known that children with cystinosis may have crystalline deposits in the cornea. In only a few cases had the cornea been examined histologically (Bürki, 1941; Streiff, 1948; van Canneyt and Kluyskens, 1948). The lesions are especially well seen by using polarized light.

II. Cutaneous diseases

There are relatively few histologic reports concerning primitive corneal degenerations which may accompany hereditary skin affections (genodermatosis)

A. Epidermolysis bullosa dystrophica

There are many publications dealing with the changes of the lid and conjunctiva which accompany typical alterations of the skin in the dystrophic form of epidermolysis bullosa. In addition to the involvement of the lids and conjunctiva, the more recent literature describes corneal changes characterized by recurrent erosions followed by diffuse parenchymal edema. This results in interlaced corneal scars in benign cases and in destruction of the cornea with perforation in more severe cases.

The only histologic examination of corneal changes that we have found in the literature is that of Cohen and Sulzberger (1935).*

Case report

We have had the opportunity of performing a corneal biopsy on a little girl suffering from severe epidermolysis bullosa dystrophica presenting typical corneal changes.

Case 4 (Clin. 11731/57, M. . . . Chantal, born, 1955†)

A sister, aged one year and a half, shows the same cutaneous affection, but more benign. There are no other brothers or sisters. Family history presents no peculiarities. No consanguinity.

Slitlamp examination. The surface of the cornea is irregular. It presents a diffuse, spotty, and granular clouding localized in the epithelium and Bowman's membrane (fig. 6).

Histologic examination. In the epithelium of the corneal fragment there is a fairly marked vacuolization, especially in the basal cells, and, in places, a slight cellular dissociation. In general the epithelium adheres rather poorly to the underlying tissue; it is even absent in places. The structure of the stroma is normal (fig. 7).

B. Keratosis follicularis spinulosa decalvans (Siemens)

The almost generalized cutaneous lesions in this disease are characterized by a multitude of follicular spines which, when

* In 1913 deSchweinitz discussed the possible histologic changes of the cornea in epidermolysis bullosa; we would like to emphasize, however, that his considerations were not based on histopathologic examination of the cornea. In this atypical and very advanced case, the corneal tissue was very severely altered and consequently gave no information about the early specific lesions.

† This case was presented at the meeting of the Swiss Dermatological Society, October 12 and 13, 1957. (Dermatologica, **116**:332, 1958.)

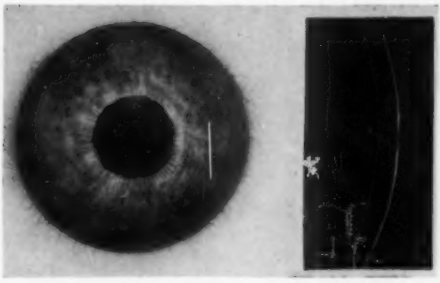

Fig. 6 (Forgács and Franceschetti). Biomicroscopic appearance of corneal changes in a case of epidermolysis bullosa dystrophica. (Personal obs., Case 4, L.E.)

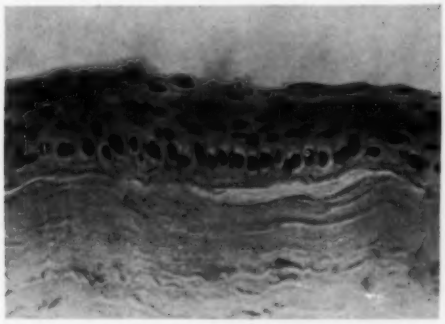

Fig. 7 (Forgács and Franceschetti). Epidermolysis bullosa dystrophica. Histologic picture of the cornea (same case as figure 6). Marked vacuolization of the basal epithelial cells. Interruption of Bowman's membrane in places.

touched, give the impression of a nutmeg grater. Besides a partial loss of the eyebrows on the temporal side (sign of Hertogh), it is possible to find a secondary baldness of the neck. The ocular disturbance which may accompany this cutaneous disease is characterized by intense photophobia caused by the superficial corneal changes.

Siemens considered the corneal changes with superficial degeneration as being a secondary phenomenon resulting from rubbing by the hardened spines. Our own extensive studies of this disease indicate that the corneal changes are certainly a primary alteration (Franceschetti, et al., 1956, 1957; Sendi, 1957).

We are dealing with a sex-linked inheritance of intermediary type (abortive form in female carriers).*

Case reports

The following observation concerns the case in which Franceschetti, Jaccottet, and Jadassohn were able to give, in 1957, the first histologic description of the cornea in keratosis follicularis spinulosa decalvans (Siemens).

Case 5 (Clin. 12.402/56, H. . . . Jean-Daniel, born, 1945)

Slitlamp examination. Superficial, diffuse dust-like opacities with very regular invasion of the vessels (superficial circular pannus) are seen (fig. 8).

Histologic examination. The epithelium is thickened and of irregular structure. The basal cylindric cells are often missing. The most characteristic alteration is the presence of numerous unicellular or bicellular vesicular formations, situated most often in the superficial layers of the epithelium. They are also found here and there in the deeper layers. The cells which constitute these vesicles have a pyknotic nucleus and a slightly more acidophilic protoplasm than the other cells. Some of these vesicles have burst. The Hotchkiss-McManus (PAS) stain shows the presence of numerous small brown-orange granulations in the epithelium, apparently intracellular. They are found in all levels of the epithelium, but not outside of it. Of the other stains only the May-Grünwald-Giemsa shows the basophilic granulations. Bowman's membrane is destroyed nearly everywhere but the basal membrane of the epithelium is easily recognized. In place of Bowman's membrane are found some small cellular accumulations and, near the limbus, vessels, located in the anterior layers of the stroma. The rest of the parenchyma does not show any other abnormality (fig. 9).

The following observation concerns the case in which Franceschetti, et al., described the biomicroscopic appearance of the cornea in 1956.

* Thanks to the kindness of Dr. J. H. Jonkers, we have been able to confirm that in the large Dutch family described by Lameris-Rochat-Siemens-Holthuis and Jonkers (see Sendi for genealogic table), the hereditary, sex-linked transmission is not recessive but also intermediary since the female carriers generally have the cutaneous affection and sometimes even corneal changes. According to our personal observations, the corneal affection, in heterozygotes, is rather similar to the hereditary recurrent erosion of the cornea described by one of us (Franceschetti, 1928).

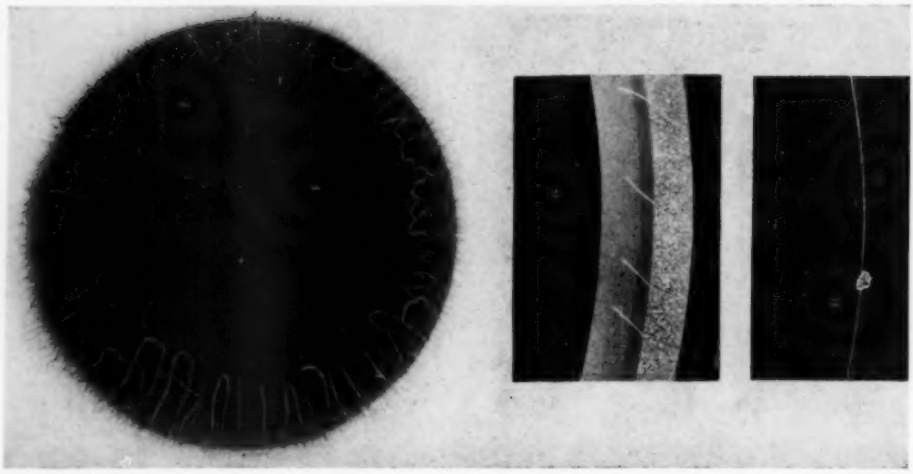

Fig. 8 (Forgács and Franceschetti). Appearance of the cornea in a case of keratosis follicularis spinulosa decalvans (Siemens). Superficial disseminated punctate opacities, circular peripheral pannus. (Personal obs. Case 5, R.E.) On left side, general view; on right side, the changes as seen with the wide and narrow beam of the slitlamp.

Case 6 (Clin. 11.900/55, F. . . . Jean-Paul, born, 1944)

Slitlamp examination. A peripheral vascularization in the form of circular pannus is noticed in both eyes. The superficial layer of the cornea is greatly altered, slightly farinaceous, and shows small subepithelial infiltrations, especially in the left eye. The parenchyma is undamaged (fig. 10).

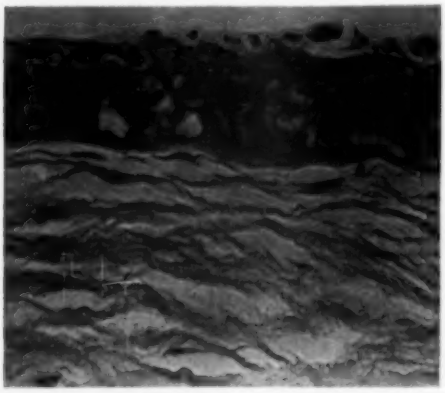

Fig. 9 (Forgács and Franceschetti). Keratosis follicularis spinulosa decalvans (Siemens). Corneal biopsy (the same case as figure 8). Irregular structure of the epithelium. Vesicular formations of epithelial cells with pyknotic nuclei, especially at the surface, some of which are ready to burst. Basal membrane easily visible; absence of Bowman's membrane. (May-Grünwald-Giemsa, ×353.)

*Histologic examination.** The epithelium has a relatively regular thickness. Nevertheless, the presence of fairly numerous vacuolated cells is noted. Certain of these vacuoles are situated at the surface and have burst; others are found in the deeper layers. They are more frequently present in the basal than in the middle layers. These vesicular formations have a very marked eosinophilic content and sometimes include the remnants of pyknotic nuclei. Furthermore, the small intracellular, strongly basophilic granules are found in all the layers, and indeed it seems that the primary lesions are composed of these small basophilic elements which stand out in strong contrast to the eosinophilic ground substance. These changes are most visible with the May-Grünwald-Giemsa and the toluidine blue stains (fig. 11). With resorcin-fuchsin there are no granulations. Bowman's membrane is regular and well preserved. The stroma has a normal structure. The basal membrane of the epithelium, well colored by PAS, is thickened and shows pseudopodlike formations, which penetrate between the cylindric basal cells. The superficial layers are also stained with PAS, especially around the vesicular formations (fig. 12).

C. Keratosis palmaris and plantaris

In spite of the frequent occurrence of keratosis palmo-plantaris, there are only a few publications concerning dystrophic

* We would here like to thank Dr. R. Rossano of Paris who has been kind enough to send us several slides of the corneal disc which he removed while doing a keratoplasty.

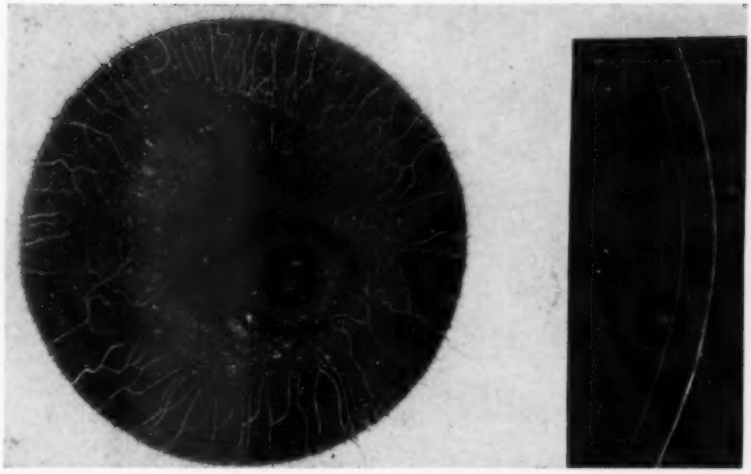

Fig. 10 (Forgács and Franceschetti). Keratosis follicularis spinulosa decalvans (Siemens). Appearance of the cornea. Very marked circular pannus. Superficial dustlike cloudiness. (Personal obs., Case 6, L.E.) On the left side, general view; on the right side, view with the narrow slitlamp beam.

changes of the cornea. One reason for this may be the fact that the common form of keratosis palmo-plantaris (Unna-Thost) does not seem to be accompanied by corneal degeneration. In analogy with epidermolysis bullosa, corneal alterations are found only in the rare recessive forms of keratosis palmo-plantaris. Furthermore the corneal changes are in general only visible by slit-lamp examination.

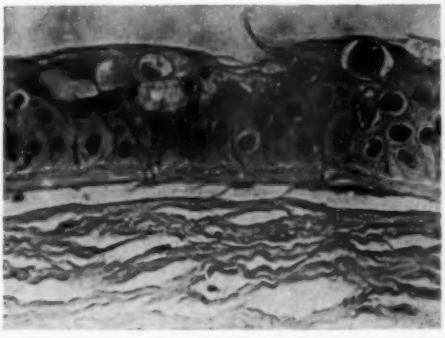

Fig. 11 (Forgács and Franceschetti). The same case as in Figure 10. Vesicular formations foremost in the superficial layers of the epithelium, one of those seems to have burst. (May-Grünwald-Giemsa, ×353.)

In the older literature only two authors have described the histologic changes in the cornea. Both cases were very similar and the corneal alterations were macroscopically

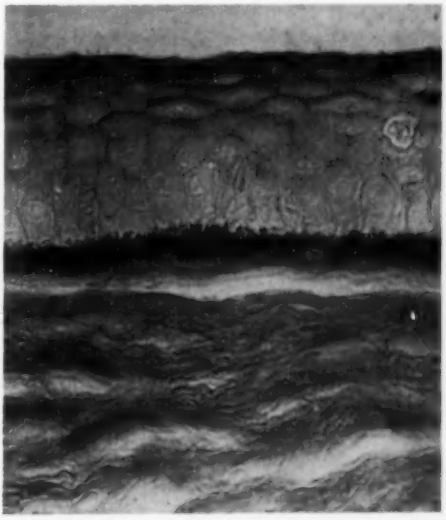

Fig. 12. (Forgács and Franceschetti). The same case as in Figure 11 PAS. The well-stained, thickened basal membrane of the epithelium shows pseudopodlike formations.

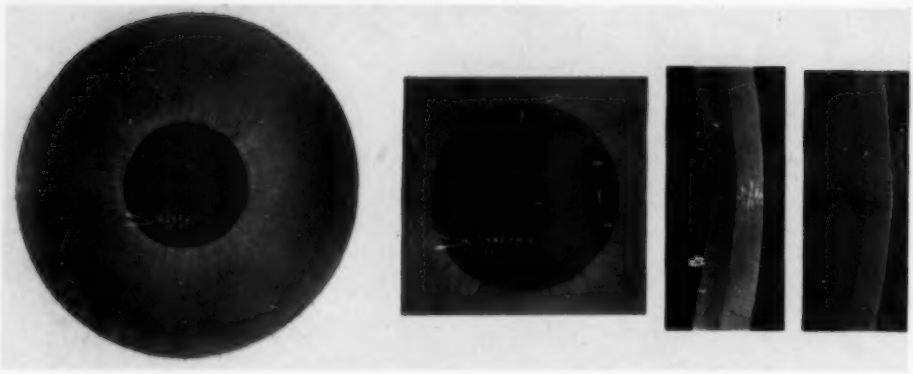

Fig. 13 (Forgács and Franceschetti). Biomicroscopic appearance of the superficial herpetiform changes of the cornea in a case of disseminated keratosis palmo-plantaris. (Personal obs., Case 7 (R.E.)

visible (Brünauer, 1924; Spanlang, 1927). Histologically there were formations of perinuclear vacuoles and keratinization of the superficial layers. Besides this Bowman's membrane was absent and replaced by a loose connective tissue, rich in cells.

Richner (1938) first drew attention to the fact that in general corneal changes accompanying keratosis palmo-plantaris can only be discovered with the slitlamp, in spite of the fairly well-pronounced subjective disturbances (photophobia, periods of pain, as in erosions). The corneal condition is characterized by its herpetiform aspect.

A similar case was afterward described by Hanhart (1947). He stressed the fact that in his case as well as in that of Richner, the keratosis palmo-plantaris was accompanied by oligophrenia. We have been able to confirm the characteristic herpetiform appearance of the corneal degeneration in two familial cases (sister and brother) of keratosis palmo-plantaris. As in Hanhart's case, they were the issue of a consanguinous marriage.

Case report

We have had the opportunity to perform a corneal biopsy on one of our cases.

Case 7 (obs. Clin. 13501/58, L. . . . Elena, born, 1949)

Like her brother, who is five years of age, this child has painful hands and feet, which present a disseminated palmo-plantar keratosis, with pronounced clavi. She also has severe eye symptoms (photophobia, pains, lacrimation, and so forth).

Slitlamp examination. There are superficial herpetiform opacities in the center of the cornea in both eyes (fig. 13).

Histologic examination. The stroma does not show any abnormality. Bowman's membrane is present everywhere and of a regular thickness. There is no hyperkeratosis of the epithelium but there are some rare vacuolated cells; on some sections the basal layer is thinner than normal. The lesions which are probably responsible for the clinical symptoms are found in the middle and deep layers of the epithelium. They consist of de-

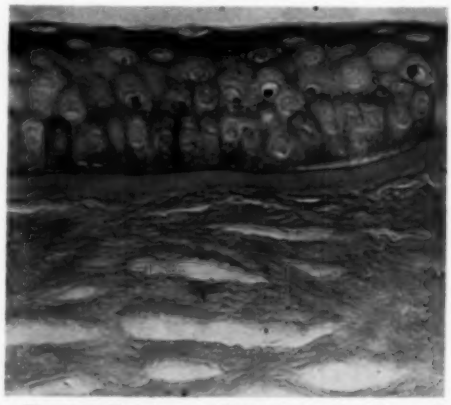

Fig. 14 (Forgács and Franceschetti). Keratosis palmo-plantaris. Corneal biopsy. The same case as Figure 13. Small intracellular granulations are recognized in the middle layers of the epithelium. Some are in direct contact with Bowman's membrane (in the right side of the figure). The latter is well preserved. (PAS, ×353.)

posits, strongly colored by McManus, which are found in the middle layers of the epithelium and also in direct contact with Bowman's membrane (fig. 14). With other stains such as resorcin-fuchsin it is also possible to discern the presence of these granulations.

D. Rothmund's syndrome

In Rothmund's syndrome (infantile poikiloderma with cataract) a band-shaped degeneration of the cornea is sometimes observed. In Franceschetti and Maeder's case (1949) the patient had had a cataract extraction, but in the family described by Rothmund some unoperated cases also showed band-shaped degenerative changes.

The histologic appearance of the cornea in the above mentioned case has been published by Franceschetti and Babel (1950).

E. Ichthyosis vulgaris

Unfortunately we do not yet possess histologic material from cases with this disease. It may be of interest here to underline that it is possible to find either a deep dystrophy of the cornea or a band-shaped degeneration (Franceschetti and Schläppi, 1957). Derrick Vail gave a clinical and histologic description of a case of corneal involvement in congenital ichthyosis, as well as a review of the literature (1940).

F. Pityriasis rubra pilaris (Lichens acuminatus)

This disease is characterized by follicular hyperkeratosis. Corneal alterations are uncommon. Only Komoto (1909) has described the histologic changes in the cornea. He found keratinization of the epithelium more pronounced in the limbal region, a vascularized subepithelial connective tissue, rich in cells, and absence of Bowman's membrane. The changes found by Komoto are very similar to those reported by Brünauer in his case of keratosis palmaris and plantaris.

Summary

We have described the biomicroscopic and histologic appearance of the corneal alterations in three familiar cases of gargoylism and have given the first histologic description of the primary corneal lesions in a case of epidermolysis bullosa dystrophica.

Furthermore, we have been able to study the histologic changes of the cornea in two cases of keratosis follicularis decalvans (Siemens). Finally we have described, for the first time, the histologic appearance of the herpetiform corneal lesions which are found in the special recessive type of disseminated keratosis palmo-plantaris with oligophrenia (Richner-Hanhart type).

In all our cases we found that staining with PAS was very useful for the detection of tissue alterations resulting from metabolic disorders.

Clinique Ophtalmologique Universitaire.

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PREPUBERTAL INTRAOCULAR MALIGNANT MELANOMA*

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INTRODUCTION

Malignant melanoma of the uvea is the most commonly occurring intraocular malignant tumor in adults.

The literature would indicate that prepubertal malignant melanoma of the uvea must be exceedingly rare. They have been mentioned in the literature,[2, 15] but no well-documented cases are presented.

Twenty malignant melanomas, occurring before puberty, involving the eyelids and other parts of the body have been reported by Nowkirischky,[11] Reese,[15] Allen and Spitz,[1, 19] Coe,[3] Coffee and Berkeley,[4] Dobson,[5] Fuste and Mora-Morales,[6] Hendrix,[7] MacDonald,[8] McWhorter and others,[9, 10] Russo,[16] Truax and Page,[20] Webster and others,[20, 21] Williams,[22] and Wright.[23] The preceding cases do not include those of transplacental transmission which are not germane to this discussion.

* From the Estelle Doheny Eye Foundation, Los Angeles.

placed by the neoplasm. The tumor contains ex-

Malignant melanomas occurring before puberty should not be confused with juvenile melanomas which are rapidly evolving lesions occurring usually in late puberty or adulthood. Juvenile melanomas are rapidly growing compound nevi with histologic features of hyperplasia and anaplasia;[17] they are always benign. The confusion between skin lesions of benign juvenile melanoma and prepubertal malignant melanoma has resulted apparently in the advocacy of less radical surgery in malignant pigmented lesions before puberty.[12, 13, 19, 21] More recently it has been emphatically stated that malignant melanomas in childhood are just as dangerous as those in adulthood, and should be treated similarly. The two do not differ clinically or histologically.[1, 5, 9, 10]

The following two cases are presented as malignant melanomas of the uvea occurring before puberty.

Case reports

Case 1

A five-year-old Mexican boy was noted to have esotropia for three months. The right eye was normal. The anterior chamber of the left eye was shallow. The iris and pupil were not remarkable. The lens was clear. A dark, solid, pigmented mass was seen protruding from the lower portion of the ciliary body. The retina was detached over this mass. A diagnosis of pigmented tumor, arising from the ciliary body, was made.

Fig. 1 (Cury, Lucic, and Irvine). *Case 1.* Prepubertal intraocular malignant melanoma apparently arising from pigment epithelium of the retina (×10).

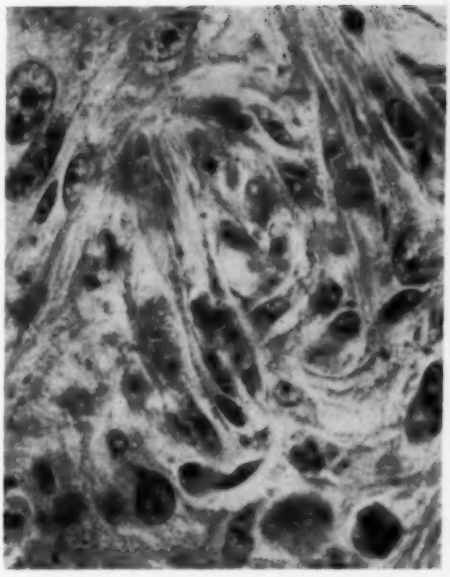

Fig. 2 (Cury, Lucic, and Irvine). *Case 1.* Prepubertal intraocular malignant melanoma, showing extreme pleomorphism, abnormal mitotic figures, and tumor giant cells (high power).

Gross description. The cornea is transparent. The epithelium is intact.

The eyeball was opened vertically, the larger calotte taken temporally. The anterior chamber is of normal depth. A small, yellow lens is in place and is adherent to the posterior surface of the iris. Temporally, a deeply pigmented tumor mass arises in the choroid and fills the vitreous cavity, except for a small area superiorly. The mass is adherent and encircles the lens anteriorly and measures 16 by 17 mm. in the region of the large calotte. At the nasal calotte the mass is bilobed and fills the vitreous cavity inferiorly and posteriorly. The retina is detached over the mass. A clear coagulum fills the balance of the vitreous cavity.

Microscopic description. The cornea is not remarkable, except for some focal thinning of its epithelium. The anterior segment is essentially normal.

Of primary interest is a heavily pigmented tumor filling the inferior half of the vitreous cavity and extending from the anterior insertion of the ciliary body to within four mm. of the optic disc. The overlying retina is invaded by tumor, and at the ora serrata the tumor apparently erodes through the retina. The stroma of the orbicularis ciliaris, the pars plana, and the adjacent choroid are re-

placed by the neoplasm. The tumor contains extensive areas of necrosis and is moderately vascular. Foci of densely packed pigment-laden phagocytes are noted. Tumor cells invade the blood vessels. In bleach sections, the neoplasm is seen to be extremely pleomorphic, and the cells vary considerably in the intensity of their staining reaction. Abnormal mitotic figures and tumor giant cells are seen.

The subretinal space between the tumor and the disc is filled with serum and heavily pigmented cells thought to be phagocytes. The retina is separated above, and the serum beneath it contains pigment-laden phagocytes. In some areas, particularly adjacent to the tumor, the pigment epithelium appears to be proliferating, forming small nodules that may represent phagocytes or tumor. The adjacent sclera appears to be invaded by neoplasm equatorially. There is no obvious evidence of extrabulbar extension in the sections examined.

Opinion. Malignant melanoma of choroid and ciliary body. Separation of retina secondary to intraocular melanoma.

CASE 2

An 11-year-old white boy had had a decrease in vision in the left eye for two years. A diagnosis of malignant melanoma, located between the disc and the macula, was made a year ago when the boy was 10 years of age. At that time he had had symptoms for two years, indicating that his lesion first produced symptoms when he was eight years of age. An operation was refused and, since that time, the patient has been under the care of a naturopath. In June, 1955, the eye became blind, glaucomatous, and painful, and for this reason it was removed.

At the time of enucleation, the cornea was edematous. There was a four-plus ciliary injection.

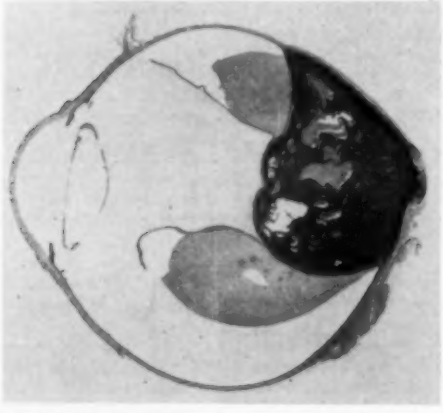

Fig. 3 (Cury, Lucic, and Irvine). *Case 2.* Prepubertal intraocular malignant melanoma arising from choroid with extension into optic nerve (×10).

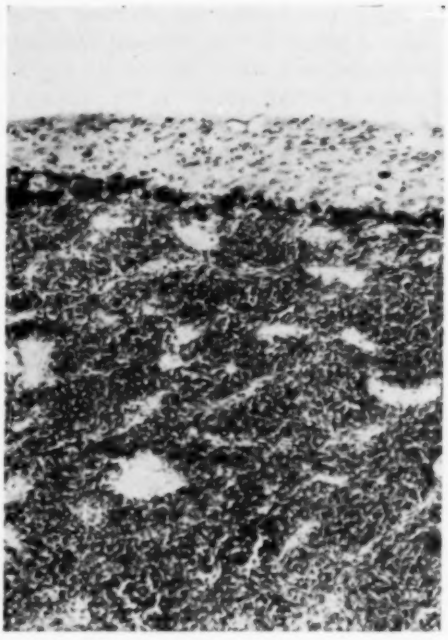

Fig. 4 (Cury, Lucic, and Irvine). *Case 2.* Prepubertal intraocular malignant melanoma penetrating Bruch's membrane (low power).

The anterior chamber was deep. There was a three-plus flare and a large number of circulating cells. The pupil was dilated and fixed. There appeared to be a marked ectropion uveae. Vessels were seen on the anterior surface of the iris. The lens was clear. The vitreous was cloudy. A dark, smooth, rounded mass was seen in the vitreous, but all further details were obscured.

Gross description. The specimen is a left eyeball, measuring anteroposteriorly 26 mm., horizontally 24 mm., and vertically 24 mm. The sclera is blue-white in color. The optic nerve is three-mm. long. There is a small area of pigmentation adjacent to the nerve superiorly and nasally. By transillumination, a shadow, 20 mm. in diameter, is seen surrounding the optic nerve. The diameter of the nerve is greater than normal. The area between the sheath measures six mm. A small, bluish spot is present on the sclera just above and slightly nasal to the nerve. The cornea is translucent. The epithelium is intact.

The eyeball was opened horizontally, the larger calotte taken superiorly. The anterior chamber is shallow. A flat, yellow lens is in place. Posteriorly a large, pigmented mass arises in the choroid and extends forward to the midline of the vitreous cavity. The mass measures 12 mm. anteroposteriorly and 16 mm. horizontally in the region of the large calotte.

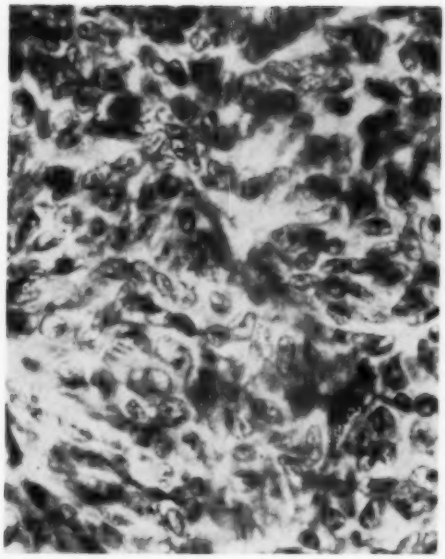

Fig. 5 (Cury, Lucic, and Irvine). *Case 2.* Prepubertal intraocular malignant melanoma of choroid, showing varied cytology (high power).

The retina is separated nasally over the tumor. The vitreous cavity and subretinal space are filled with a translucent, green coagulum.

Microscopic description. A pigmented mass is seen to arise in the choroid posteriorly and to occupy most of the posterior segment. It mushrooms through the lamina vitrea and lies beneath the retina. The latter is thinned and atrophic and has lost the normal arrangement of its nuclear layers. The adjacent retina is separated. The tumor has extended via the nerve through the globe to lie in the episclera posteriorly. Histologically the lesion is composed of a variety of cells ranging from spindle A to epithelioid; many of these are arranged in fascicles. There are large serous lakes and large areas of free blood within the neoplasm. There is considerable necrosis. Anteriorly the ciliary body is atrophic. The iris leaves are retracted. A newly formed vascularized membrane is seen on the anterior surface of the iris, producing an ectropion uveae. The lens is not remarkable. The cornea is comparatively clear.

Opinion. Malignant melanoma of the choroid, mixed cell type, with extrabulbar extension. Separation of the retina secondary to intraocular neoplasm. Glaucoma secondary to intraocular neoplasm. Intraocular hemorrhage secondary to necrosis of intraocular tumor.

Discussion

The histopathology of the tumor in the first case is particularly interesting because of the hyperplasia and apparent dysplasia of the pigment epithelium. Although its origin could not be proven, it is of interest that many ophthalmic pathologists, about 50 percent of those polled, felt that this represented a malignant melanoma arising from the pigment epithelium of the retina.

If so, the lesion is unique, as this is the first case of malignant melanoma arising from the pigment epithelium of the retina. It is amazing that the pigment epithelium of the retina which shows such an ability to proliferate and to undergo metaplasia does not more frequently show neoplasm. This patient is alive and well one and one-half years after enucleation.

The second case is unusual by virtue of its extension along the nerve. At the present time the child exhibits central nervous system involvement, presumably by extension of the malignant melanoma. The histology of this lesion is entirely similar to those occurring in adults. Therefore, the surgical treatment of uveal malignant melanomas occurring before puberty should be the same as of those of adulthood.

Summary

Two cases of prepubertal intraocular malignant melanomas with pathologic findings are presented. One of the tumors is unique in that it apparently originates from the pigment epithelium of the retina.

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UNILATERAL EXOPHTHALMOS FROM INTRACRANIAL LESIONS*

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Unilateral exophthalmos always presents a problem to the physician. It demands careful evaluation by members of several different medical specialties and even then the exact etiology cannot always be assigned. There are at least 50 known causes for unilateral exophthalmos but for convenience in this presentation we can list the principal causes as: (1) the endocrine group, (2) the orbital pathology group, and (3) the intracranial pathology group.

Theoretically it seems easy to diagnose exophthalmos of endocrine origin. However, this is not always the case especially where the exophthalmos is more advanced on one side than the other. It has been stated by most observers that asymmetry is common in the thyrotropic type of endocrine exophthalmos. In the more common type of endocrine exophthalmos, Graves' disease or exophthalmic goiter, the exophthalmos is usually equal in each eye and accompanied by the classical local signs such as lid lag and staring, and of course the usual systemic signs and symptoms of thyrotoxicosis. The thyrotropic type is more complex in its initiating cause or causes, difficult to diagnose early, and not easy to treat.

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The orbital causes of exophthalmos are many and varied. They range from primary malignancies to myopia. As with the endocrine group it is not always easy to assign a definite etiologic factor without considerable study. The most common orbital causes are hemangioma, pseudotumor, and mucocele. It is to be remembered, though, that malignancies are all too common. Pfeiffer[1] in his monograph on radiologic diagnosis of exophthalmos gives a 10-percent incidence to malignant orbital neoplasms. Six percent were primary and four percent secondary. Drescher and Benedict,[2] in a series of 177 cases of asymmetric exophthalmos, found 21.5 percent due to malignant orbital lesions and this figure compares with Reese's[3] in his series of 153 orbital tumors.

As Pfeiffer[1] says: "The greatest cause for alarm in exophthalmos is the possibility that it may be caused by a malignant growth."

Turning to the intracranial causes of unilateral exophthalmos we have a picture vastly different from the orbital one. Instead of many individual causes, 25 in the orbital group, we have few intracranial causes. If we then separate these into pulsating and nonpulsating, we have an even easier time making a presumptive diagnosis.

It might be well to review the points that should be covered in order to evaluate a case of unilateral exophthalmos:

1. A history which can place the probable time of onset and the progress, together with associated symptoms of pain in or about the eye or headache, should be taken.
2. Vision and external examination should be made.
3. The amount of exophthalmos should be measured as well as the width of the palpebral fissures and size of the pupils.
4. Ocular motility should be tested—diplopia fields, muscle balance, convergence, accommodation.
5. Orbital resistance to direct pressure and orbitonometry should be done.
6. Ophthalmoscopic examination and refraction are necessary to evaluation.
7. Intraocular pressure should be taken.
8. Visual fields, central and peripheral, should be charted.
9. The orbit should be palpated.
10. A physical examination should be performed.
11. Laboratory tests should be made.
12. There should be X-ray studies of the orbits, optic foramina, sinuses, and skull.
13. Photographs of the eyes should be taken.

There are several of these points which need amplification, one being an accurate measurement of the amount of exophthalmos. This measurement is not always as exact as we would like it to be, though with practice a given examiner can get fairly consistent results.

Another point that needs to be stressed is the width of the palpebral fissure. It is common to think of exophthalmos as being associated with retraction of the upper lid, giving the appearance of staring. However, this sign is found only in the edocrine type, now classified as thyrotoxic. The progressive type of endocrine exophthalmos—the presently designated thyrotropic—presents a normal nonspastic upper lid. The exophthalmos due to an intracranial pathologic alteration also shows a flaccid upper lid and often gives the impression of a pseudoptosis.

Ocular motility tests aid a great deal in the differential diagnosis of exophthalmos and are naturally of importance in following the progress of a given case. In the exophthalmos of intracranial origin there is rarely any disturbance of motility and, if present, it is a very late sign and usually means actual invasion of the orbit. There is often interference with motility in thyrotoxic exophthalmos, and convergence may suffer if associated with myasthenia. Also this type is bilateral, of low degree, and there are many associated signs. The progressive type, however, while probably always bilateral, may be asymmetric to a degree resembling unilateral exophthalmos.

It is in this type that we find disturbances of ocular motility manifest as gaze palsies. A limitation of motion in one direction or another is more common than a definite single paresis. The most common one that I have seen is a monocular loss of upward gaze. In orbital tumors a limitation of motion in one direction or another is also a not uncommon finding.

The next test that should be stressed is the test for orbital resistance. As would be expected, there is normal resistance in Graves' disease, an increased resistance in the exophthalmos of progressive exophthalmos, and in orbital tumors or pseudotumors. In exophthalmos of intracranial origin there is always increased resistance. This is true whether there is actual encroachment of the orbital space by tumor or decrease in orbital volume by (1) pressure on the roof or walls or (2) by exostoses.

The measurement of orbital resistance is not usually a very exact one. It is equivalent to taking digital tension—extreme limits are easily discovered and correctly described but borderline pressures need a more exact test. Also, if one is to make a series of examinations over a period of time, an accurate objective test is of real value. An instrument for orbitonometry was first introduced by Langenhan[4] in 1910. The test has never become popular, however. Orbitonometry probably has its greatest use in showing that a pseudo-unilateral exophthalmos is really an asymmetric bilateral exophthalmos. An increased resistance bilaterally points to an underlying endocrine dysfunction even though classical signs and symptoms are absent. As shown by Copper[5] and others, increased orbital resistance occurs early in thyrotropic exophthalmos and this may be the only clue to the etiology at this stage. In the conditions which are the subject of this paper there is a unilateral increased resistance in orbital resistance. As in the thyrotropic cases the increased resistance undoubtedly precedes the proptosis and this should offer a fertile field for further study.

Ophthalmoscopic examination need not be stressed here. It is an examination carried out by all physicians performing a complete physical examination and the examination of the optic disc is done well and interpreted correctly. The signs that concern us here are edema of the disc and atrophy of the disc. While we associate primary atrophy with chiasmal lesions, we must remember that other intracranial lesions can produce this sign. Since it takes a meningioma of the frontal region a long time to produce increased intracranial pressure, papilledema is not a common sign in tumors in this area.

Visual fields are not so revealing in the lesions we are considering here as they are in other intracranial space-consuming defects. However, a unilateral exophthalmos combined with a field defect, usually a central scotoma on one side only, is certain to lead to an optic atrophy if the cause is not eliminated. Also fields are necessary to insure the fact that the visual pathways—the nerves, chiasm, tracts, and radiations—are intact.

Palpation of the orbit is not as helpful as we would wish in unilateral exophthalmos. If palpation is positive, one is then confronted with the question of whether or not the mass is confined entirely to the orbit. In a series of 24 cases reported by Dandy[6] in 1941, only 25 percent were strictly orbital. This is in agreement with other authors.

X-ray studies of the orbits, optic foramina, sinuses, and skull are just about the most important single modality that can be employed. Most authors who mention X-ray diagnosis agree that about half the cases of intracranial meningiomas can be diagnosed by X-ray films alone. The percentage of cases of unilateral exophthalmos from all intracranial causes that can be diagnosed by X rays is even higher. This is because the onset of the exophthalmos is relatively late in the course of the disease even though it may be the presenting symptom.

The classic article on X-ray diagnosis of exophthalmos was written by Pfeiffer.[1] In

a series of 200 cases of exopthalmos, both bilateral and unilateral, there were positive X-ray findings in 138. Of these positive films there were 84 that were either completely diagnostic or clearly indicative. Percentagewise the diagnostic-indicative group is 42 percent.

Of the intracranial causes of unilateral exophthalmos the meningiomas play the most prominent role. In most series of cases they occur as the etiologic factor as often as all the other causes combined. Next most common are gliomas of the optic nerve or chiasm. Arteriovenous aneurysm, usually traumatic, and usually a communication between the internal carotid and the cavernous sinus is also fairly common. A rare cause is a sacculated aneurysm of the internal carotid. There are a few cranial causes of unilateral exophthalmos such as ethmoid-orbital osteoma and neurofibromatosis.

The meningiomas

Anyone who brushes against the literature on meningiomas, however lightly, must come away with a feeling of awe for Harvey Cushing.[7] Not only did he bring order out of chaos in the meningiomas but his articles seem to lift one up out of the doldrums of the mass of medical literature. His writings are so extremely readable and have the elements of suspense and instruction expertly compounded. His papers and monographs can be recommended for serious study and also for light summer reading.

The first report of a meningioma causing unilateral exophthalmos was that of F. Durante[8] in *The Lancet* in 1887. He cited a case of unilateral exophthalmos of three months' duration with normal ocular motility. Because of some loss of memory and loss of the sense of smell, an intracranial etiology was suspected and, after removal of a large area of the left frontal bone, the tumor was encountered and removed. It was said to be a sarcoma, a diagnosis sometimes made of this type of tumor until the 1920s. Because of its large size and the pathologic diagnosis it was probably a meningioma and may have arisen from the olfactory groove. It is not common for olfactory groove tumors to produce exophthalmos but any tumor on the floor of the anterior fossa could be responsible. The roof of the left orbit was pushed downward by the tumor but there was no evidence that the orbit had been entered. Incidentally this is the first report of the removal of an intracranial meningioma with recovery.

Another early report was that of T. H. Weisenburg[9] of Philadelphia in the *J.A.M.A.*, in 1910. The paper, entitled "Exophthalmos in brain tumor," reported on eight cases. Three of these were unilateral and the exact mechanism of the exophthalmos was as controversial then as it is now. The cause in two of the unilateral cases was said to be increased intracranial pressure and in the third case direct pressure on the cavernous sinus. There must have been a fairly lively hassle going on in Philadelphia at the time for deSchweinitz[10] was present at the autopsy in this third case in order to learn, if possible, the cause of the exophthalmos. The tumor, by the way, was a large middle fossa "sarcoma" which we now know as a form of meningioma, and deSchweinitz showed conclusively that there was no direct pressure on the cavernous sinus.

The other two cases in which the exophthalmos was said to be due to increased intracranial pressure perhaps could have been explained more satisfactorily. It is hard enough to believe that a bilateral exophthalmos could be ascribed to increased intracranial pressure let alone a unilateral case. However, it occurs throughout the literature as a possible direct etiologic factor—even in the absence of a pathologic connection between the orbit and cranial cavity.

Elsberg, Hare, and Dyke[11] in an article on unilateral exophthalmos in intracranial tumors, in 1932, made this statement: "It is doubtful if there can be venous stasis

enough to produce exophthalmos by an increase of pressure in the middle cranial fossa. We are inclined to the view that the rise of pressure is transmitted to the orbital contents through the superior orbital fissure and that the exophthalmos results from this increase of pressure upon the contents of the orbit." This is probably true for tumors confined to the middle fossa. However, Elsberg, Hare, and Dyke believe the protrusion may be due to a perforation of the tumor into the orbit, to thickening of the orbital walls, or extension of the growth through the superior orbital fissure.

Meningiomas probably arise from clusters of arachnoid cells at any place where these cells exist. There are several areas around the orbit which are common sites of origin. Cushing,[12] who was the first to group them together and to give them a common name, also was the first to attempt classification of the point of origin. Those arising from the sphenoidal ridge were divided into three specific areas. An attempt was made, and in the main was successful, in assigning certain signs and symptoms to meningiomas arising from specific areas of the ridge. For instance, tumors of the inner ridge (or lesser wing, clinoidal or deep sphenoidal ridge) give rise to exophthalmos in about 40 percent of cases. They also may cause some chiasmal interference.

The middle ridge group of meningiomas also is quite productive of exophthalmos. There are said to be two separate mechanisms for the exophthalmos in this particular location: (1) by direct pressure causing a caving in of the walls of the orbit, or (2) by causing hyperostosis and diminished orbital volume by thickening of walls and roof.

The outer ridge or pterional group comprise two distinct morphologic types: the enplaque variety and the global type. The enplaque tumors spread over the outer ridge and into the middle fossa, petrous ridge, and anterior fossa. They cause unilateral exophthalmos and hyperostosis and, by spreading medially, may interfere with vision. It is this type of meningioma in this location which causes palpable and visible temporal overgrowth. It is not uncommon to see a patient with unilateral exophthalmos and temporal swelling on the same side in these slow-growing more or less silent tumors.

Fig. 1 (Campion). Marked left exophthalmos and left esotropia. Exophthalmometer readings: right, 15; left, 23.

Case report

Typical of pterional meningioma of the enplaque type is the following case (figs. 1 to 6). A 59-year-old white woman was seen in the eye clinic of the University of California Medical Center in 1950, complaining of poor vision and protusion of one eye. History revealed there had been a transient turning in of the left eye 19 years before. This was presumably due to a left sixth nerve palsy that cleared but later recurred and was permanent. The unilateral exophthalmos had been present for nine years before admission and there had been poor vision in the left eye for four years.

Fig. 2 (Campion). View from above demonstrating the marked fullness of the upper lid on the involved side.

Fig. 3 (Campion). With eyes looking left there is a complete paralysis of the left lateral rectus muscle.

Examination showed complete loss of vision in the left eye due to an optic atrophy. Exophthalmometer readings were: right, 15; left, 23. The left lateral rectus muscle was paretic. There was increased resistance to pressure on the left eyeball. There was no pain in or about the eyes and the patient did not suffer from headache.

A clinical diagnosis of a meningioma of the left sphenoidal ridge was made by the eye resident who examined the patient. The patient was seen in neurosurgical clinic and hospitalized for further study and surgery. The X-ray films and arteriograms were diagnostic and a left frontal craniotomy revealed a meningioma of the enplaque type spreading like a rug over the anterior fossa, the ridge, and down into the middle fossa. The exact site of origin was not determined but it was probably of the pterional group.

This case also serves to show how long a case can go on from onset of symptoms to definitive treatment. The fact that the patient seems to live so long after the diagnosis is made, even without treatment, has led some observers to wonder if the surgical intervention is always justified. In a paper from Olivecrona's Clinic, by Castellano, Guidetti, and Olivecrona,[13] such a suggestion is made. They reported on 3,256 surgically verified brain tumors: 608 (18.4 percent) were meningiomas; 111 (18.25 percent) were sphenoidal ridge; 74 (66 percent) were pterional; 59 (79 percent) were "global"; 15 (21 percent) were "enplaque."

There were also 10 clinically verified enplaque pterional meningiomas. In these 25 cases the average age was 47 years. The youngest was 17 years and the oldest 63 years. The duration of symptoms averaged four years from onset to diagnosis. Unilateral exophthalmos was the most frequent initial complaint and occurred first in 11 cases. It developed in the remaining 14 in the course of the disease. In 64 cases collected from the literature unilateral exophthalmos finally developed in 62. In four cases of the Olivecrona series, temporal swelling was the initial symptom and it developed later in 10 others.

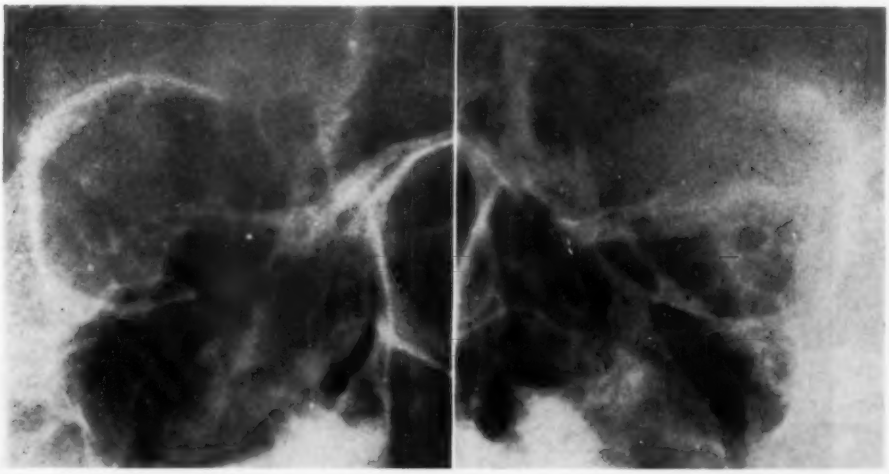

Fig. 4 (Campion). An X-ray view of the two orbits for comparison. The left optic foramen is irregular and has a much heavier margin. Entire orbit shows increased density especially of the roof and lateral wall. This means involvement of both lesser and greater sphenoidal wing.

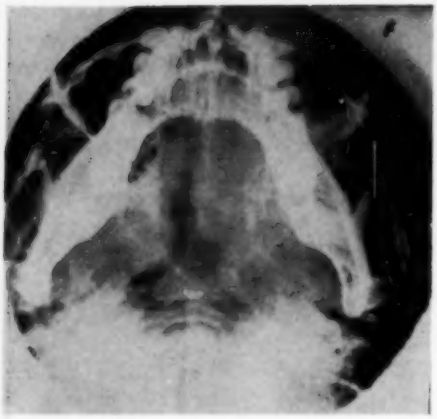

FIG. 5 (Campion). Basal view demonstrates increased density on the left with some encroachment on the nasal passages.

In the 64 collected cases just mentioned, exophthalmos was the initial symptom in 46, while temporal swelling occurred first in four. The two coincided in onset in eight cases. Headache was the first symptom in five cases of the 64 and blurred vision in four cases.

In the 25 enplaque meningiomas reported by Olivecrona and his co-workers there was a "unilateral, nonpulsating, irreducible exophthalmos." Most often the eye was pushed down and forward with edema of the eyelids. There was some limitation of motion in all directions in most patients.

Of this group 15 were operated and seven were improved; five were unimproved or worse; two died following surgery and one died a month later from a lung abscess. Of

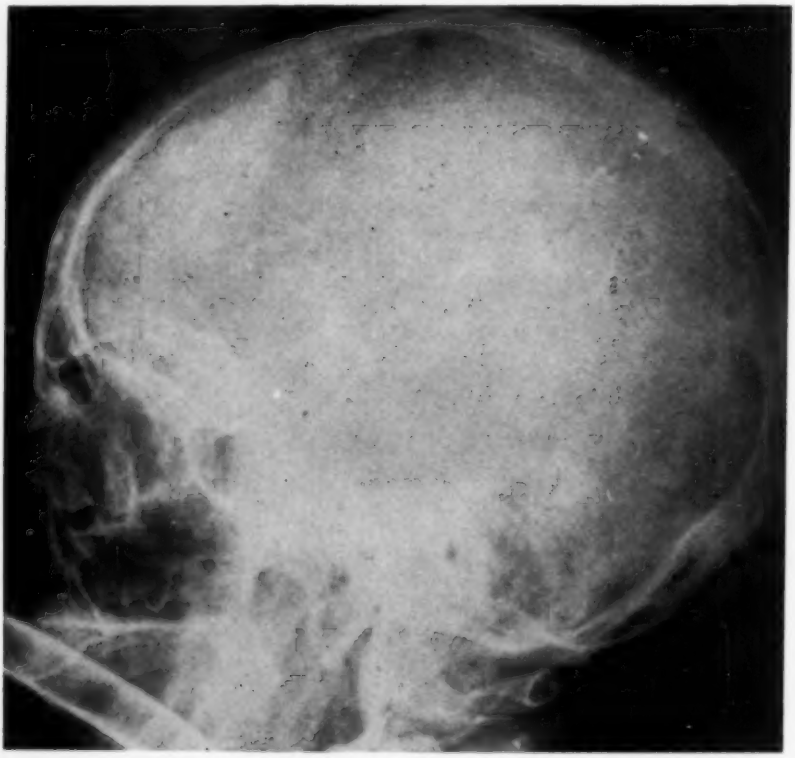

Fig. 6 (Campion). Arteriogram showing the left internal carotid artery straightened out by upward thrust of the tumor. There is also visible an arterial flush over the body of the sphenoid.

the 10 clinically verified pterional meningiomas two died intercurrently and the others were well. The question was then brought up on whether or not the pterional enplaque meningiomas should be operated at all.

Davis and Martin[14] reported a series of 754 verified and unverified intracranial tumors and among these were 15 cases of unilateral exophthalmos. Of the six verified cases, two were global and two enplaque meningiomas. One tumor was unclassified and one was a glioma of the optic nerve. Three of the patients suspected of having orbital involvement had none at operation. This again brings up the question of the mechanism of the exophthalmos and again we see that invasion of the orbit or intracranial venous stasis are not necessarily present. As Dandy[15] pointed out: "Unilateral exophthalmos is usually due to depression of the roof of the orbit by a superimposed tumor of slow growth."

Horrax and Strain[16] agree that about 15 percent of all intracranial tumors are meningiomas and that in about one fourth of these ocular signs or symptoms are the initial cause for the patients' concern. They group the eye findings together as reduced vision, double vision, and protrusion of one eye. They found the average duration of ocular findings from onset to diagnosis was 36 months in 115 meningiomas. The duration average could be reduced to 26 months if one case in which there was a unilateral exophthalmos of 20 years' duration in a sphenoidal wing meningioma were not included. Of 32 tumors producing ocular signs there were 11 cases of unilateral exophthalmos. They are in agreement with Pfeiffer[1] in stating that about 50 percent of the meningiomas can be diagnosed by stereographic skull films.

In a consecutive series at the University of California Hospital from 1937 to 1953 there were 119 meningiomas of all types and locations. These cases were both private and clinic and practically all of them were operated by either Dr. Howard Naffziger or Dr. Edwin Boldrey. Although meningiomas were thought to be tumors of adults (Dandy found no patient under 22 years of age), there were five in this series under the age of 20 years.

Of the 119 meningiomas there were 16 cases or 13.4 percent with unilateral exophthalmos. In four of these the exophthalmos was the presenting symptom. An unusual case was that of a 17-year-old boy who was said to have had a unilateral exophthalmos for seven years before admission to the University of California Hospital. A clinical diagnosis of meningioma of the right sphenoidal ridge was made and this was confirmed at surgery.

Summary

In summary, then, we find the majority of cases of unilateral exophthalmos from intracranial lesions confined to relatively few etiologic conditions. The most common single factor is a meningioma of the sphenoidal ridge of the en plaque variety. While exophthalmos may not occur until years after the actual beginning of the growth it may be the presenting symptom.

A glioma of the nerve or chiasm or both is a more distressing cause of unilateral exophthalmos. It occurs in children or young adults and is a malignancy. Because of the rapid growth they must be operated without delay. The glioma is the best argument for the transcranial approach in unilateral exophthalmos.

Arteriovenous aneurysms do not usually present too much of a problem diagnostically because of the pulsating characteristics. Sacculated aneurysm of the internal carotid can be more of a problem and will depend on angiograms for definite diagnosis.

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I am indebted to the Department of Neurological Surgery of the University of California (Dr. John Adams, chairman) for permission to study and report on their cases.

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THE INFLUENCE OF SOME INHIBITORS OF CARBONIC ANHYDRASE*

On the potassium and sodium content of the aqueous humor

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Carbonic anhydrases[12] are enzymes which catalyse mainly the reversible transformation of carbon dioxide into carbonic acid. Keilin and Mann as well as other investigators showed that these enzymes are zinc-containing proteins. The content of zinc is absolutely necessary for their efficacy; by separating the zinc the enzyme becomes irreversibly inactivated. The biologic importance of the carbonic anhydrase is not restricted to the carbonic acid metabolism of the blood; it is important, too, for the secretion of hydrochloric acid from the gastric mucous membrane as well as for the reabsorption of bicarbonate and the excretion of hydrogen ions through the kidneys. Furthermore, this enzyme influences the intraocular fluid exchange.

The carbonic anhydrases are very widely encountered; in vetebrates they are chiefly found in the erythrocytes, in the gastric mucous membrane, and the cortex of the kidney. They are also to be found in many other organs and tissues; whereas, body fluids usually do not contain them. In plants, too, enzymes of this type have been found.

The presence of carbonic anhydrase in the eye has already been proved by various investigators. This enzyme is found in the iris, ciliary body,[20] in the lens and the posterior segments of the eye. Supposedly 60 percent of the total carbonic anhydrase activity of the anterior uvea belongs to the ciliary body and 40 percent to the iris.[8]

* From the Institute of General and Experimental Pathology (Prof. Dr. A. Lindner) and the Second Eye Department (Prof. Dr. J. Boeck) of the University of Vienna.

Inhibitors of these enzymes[12] are various heavy metals, oxidizing agents and other compounds, as well as sulfonamides. Keilin and Mann were able to show that the inhibition by sulfonamides is to a large extent specific. It is notable that the carbonic anhydrase in plants is not inhibited by sulfonamides.

Inhibitors of carbonic anhydrase have been used for some years also in ophthalmology. They make it possible to decrease the abnormally high intraocular pressure. The mechanism of action, however, has up to now not been completely clarified.

Various investigators have dealt with the changes in the composition of the aqueous after administration of Diamox (2-acetylamino-1,3,4-thiadiazol-5 sulfonamide): The sodium content is not significantly influenced in the aqueous of man or rabbit.[7, 10, 14, 15, 17b] According to Franceschetti and co-workers[7] the potassium content of the human aqueous is not significantly reduced after administration of acetazolamide, though Takaoka[18] observed a reduction in successfully treated cases of primary glaucoma.

In the rabbit Diamox causes a significant decrease of the potassium content in the aqueous humor.[7, 10, 17b]

The chlorine concentration of the aqueous in the rabbit increases significantly after acetazolamide;[7, 14] whereas, it remains unalterated in the human.[7]

The bicarbonate content of the aqueous humor is significantly diminished by Diamox in man, rabbit and guinea pig.[3, 5, 7, 9, 14, 15]

Ascorbic acid[5, 14, 15] and lactic acid[4] in the aqueous of the rabbit are increased by acetazolamide. Furthermore the hydrogen ion concentration of the aqueous increases after Diamox in the rabbit,[7, 9, 15] but not in man.[7]

Appelmans and co-workers[1] observed in the rabbit after acetazolamide an increase in the content of protein in the aqueous; whereas, Boeck and co-workers[6] could not confirm this with certainty. In addition, Diamox decreases the osmotic pressure of the aqueous.[17a, 19]

Recently there have been developed new inhibitors of carbonic anhydrase, but few observations of their influence on the intraocular pressure and the composition of the aqueous are available.

Harris and co-workers[10, 11] report that dichlorphenamide diminishes in the rabbit the aqueous content of potassium and bicarbonates, whereas the amount of sodium is not changed. They found also that Diuril in low dosages does not influence the content of potassium and sodium in the aqueous of the rabbit.[10]

We could find no references in the literature concerning changes in the composition of the aqueous after administration of Neptazane, though Langham reports that the intraocular pressure in man and rabbit is lowered by this preparation.

In the present work we report the results of investigations with Diamox, dichlorphenamide (1,3-disulfamyl-4,5-dichlorobenzene), Neptazane (5-acetylimino-4-methyl-Δ2-1,3,4-thiadiazolin-2-sulfonamide), Diuril (6-Chloro-7-sulfamyl-1,2,4-benzothiadiazin-1,1-dioxid) and the preparation 5879 of Ciba (Esidrex, hydrochlorothiazide).*

Method

For the experiments we used rabbits of both sexes weighing 2.0 to 3.5 kg. Each animal was tested only once. The anterior chamber of the left eye of each animal was punctured, and immediately afterward the preparation to be tested was given parenterally (Diamox, dichlorphenamide), or orally (Neptazane, Diuril, and preparation 5879) and after a certain time the right eye was punctured.

The animals were divided into three groups.

Group 1

Control animals. After the puncture of the left eye, a number of these rabbits re-

* Merck, Sharp, and Dohme Research Laboratories, the Lederle Laboratories Division, and the Ciba Company, generously provided these preparations.

ceived 1.0 ml. per kg. body weight of an isotonic saline solution intravenously, and three hours later the right eye was punctured; the rest of this group were given by means of a gastric tube, 50 ml. water per animal, followed four hours later by puncture of the right eye.

GROUP 2

After puncture of the left eye, each rabbit received per kg. body weight 100 mg. Diamox (group 2a) or 100 mg. dichlorphenamide (group 2b) intravenously, and three hours later the right eye was punctured.

GROUP 3

After puncture of the left eye, these animals were given by means of a gastric tube, per kg. body weight 200 mg. Neptazane (group 3a), Diuril (group 3b), or preparation 5879 (group 3c) in 50 ml. of water; four hours later the aqueous humor of the right eye was tapped.

The puncture of the anterior chamber was made with a tuberculin syringe and a 20-gauge injection needle, after surface anesthesia of the cornea with a five-percent solution of cocaine hydrochloride.

The determinations of concentration of potassium and sodium were made by means of a Beckman flame fotometer model DU.

The results of the investigations are summarized in Tables 1 through 6. Within each group and subgroup the Student t-test was employed to determine whether the difference of the potassium and sodium content deviates significantly from zero.

COMMENT

According to Friedenwald's theory the difference between the osmotic pressure of the blood and that of the aqueous humor is essential for the inflow of water into the eye. The higher osmotic pressure of the aqueous is chiefly based upon a higher concentration of bicarbonates which are produced in the epithelium of the ciliary body. This bicarbonate production may, to a large extent, depend on the carbonic anhydrase activity of the ciliary body. If this enzyme is inhibited, the production of bicarbonates will decrease and subsequently the osmotic pressure of the aqueous will drop. The consequence would be a reduced inflow of water resulting in a decrease of the intraocular pressure.

Inhibition of the carbonic anhydrase in the rabbit decreases not only the bicarbonate concentration of the aqueous[3, 9, 14, 15] but also the potassium concentration.[7, 10, 17b] We can, therefore, assume that the decrease in potassium concentration will indicate the approximate extent of the in vivo inhibition of the carbonic anhydrase activity in the ciliary body of rabbits and the corresponding fall of intraocular pressure.

TABLE 1

GROUP 1: CONTROL ANIMALS

(Content of aqueous of potassium and sodium in mE/L.)

Animal Number	Potassium			Sodium		
	Left Eye	Right Eye	Difference	Left Eye	Right Eye	Difference
1	5.48	5.68	−0.20	153	153	0
2	4.40	4.51	−0.11	158	153	5
3	5.58	5.89	−0.31	148	153	−5
4	5.89	5.79	0.10	144	140	4
5	4.99	4.89	0.10	144	148	−4
x	5.27	5.35	−0.08	149	149	0
s x			±0.08			±2.02

In the first group the mean difference of the potassium content does not significantly deviate from zero ($0.50 > P > 0.10$). The average values of the sodium content of both eyes are equal.

TABLE 2

GROUP 2A: TESTS WITH DIAMOX
(Aqueous content of potassium and sodium in mE/L.)

Animal Number	Potassium			Sodium		
	Left Eye	Right Eye	Difference	Left Eye	Right Eye	Difference
1	5.17	3.40	1.77	162	148	14
2	5.48	3.84	1.64	153	148	5
3	4.89	4.15	0.74	144	144	0
4	4.99	3.48	1.51	148	144	4
5	4.99	4.22	0.77	153	153	0
$\bar{x}$	5.10	3.82	1.28	152.0	147.4	4.6
s $\bar{x}$			±0.22			±2.56

In group 2a the mean difference of the potassium content deviates significantly from zero ($0.01 > P > 0.001$). Statistically there is no difference between the two mean values of the sodium content ($0.50 > P > 0.10$).

TABLE 3

GROUP 2B: TESTS WITH DICHLORPHENAMIDE
(Aqueous content of potassium and sodium in mE/L.)

Animal Number	Potassium			Sodium		
	Left Eye	Right Eye	Difference	Left Eye	Right Eye	Difference
1	5.27	3.48	1.79	153	144	9
2	5.27	3.76	1.51	144	148	− 4
3	5.27	3.58	1.69	144	162	−18
4	5.07	3.66	1.41	153	153	0
5	4.68	3.48	1.20	163	153	10
$\bar{x}$	5.11	3.59	1.52	151.4	152.0	− 0.6
s $\bar{x}$			±0.10			± 5.09

In Group 2b the mean difference of the potassium content deviates significantly from zero ($0.001 > P$). Statistically there is no difference between the two mean values of the sodium content ($P > 0.50$).

TABLE 4

GROUP 3A: TESTS WITH NEPTAZANE
(Aqueous content of potassium and sodium in mE/L.)

Animal Number	Potassium			Sodium		
	Left Eye	Right Eye	Difference	Left Eye	Right Eye	Difference
1	5.58	3.40	2.18	144	131	13
2	4.61	2.79	1.82	144	144	0
3	4.89	3.15	1.74	148	144	4
4	4.61	2.94	1.67	158	153	5
5	4.99	2.97	2.02	144	140	4
$\bar{x}$	4.94	3.05	1.89	147.6	142.4	5.2
s $\bar{x}$			±0.09			± 2.13

In Group 3a the mean difference of the potassium content deviates significantly from zero ($0.001 > P$). Statistically there is no difference between the two mean values of the sodium content ($0.10 > P > 0.05$).

TABLE 5

GROUP 3B: TESTS WITH DIURIL
(Aqueous content of potassium and sodium in mE/L.)

Animal Number	Potassium			Sodium		
	Left Eye	Right Eye	Difference	Left Eye	Right Eye	Difference
1	5.68	5.38	0.30	144	140	4
2	4.99	4.51	0.48	148	153	−5
3	4.89	4.30	0.59	153	148	5
4	5.07	4.12	0.95	158	153	5
5	4.99	4.51	0.48	148	140	8
$\bar{x}$	5.12	4.56	70.56	150.2	146.8	3.4
$s_{\bar{x}}$			±0.10			±2.20

In Group 3b the mean difference of the potassium content deviates significantly from zero ($0.01 > P > 0.001$) Statistically there is no difference between the two mean values of the sodium content ($0.50 > P > 0.10$).

This speculation was the real inducement for our experiments. It was not intended to make exact comparative tests with the various inhibitors of the carbonic anhydrase; these would have required, among other conditions, the determination of the regression limits as well as equal dosages and modes of administration.

The method used in these investigations made it necessary to determine whether the withdrawal of the aqueous from the first (left) eye influences the potassium and sodium concentration in the other (right) eye which was punctured three or four hours later. (It is known that in the rabbit the withdrawal of the aqueous from one eye significantly lowers the protein content in the other eye's aqueous.[13]) In addition it was necessary to determine whether the intravenous administration of an isotonic saline solution or the oral administration of 50 ml. water per animal changes the aqueous concentration of the two tested ions.

The mean values of the potassium and sodium content of both eyes were in this series almost equal. The statistical evaluation shows also that the mean differences of the potassium and sodium concentration does not deviate significantly from zero. Withdrawal of aqueous from one eye does not influence the potassium and sodium concentration of the other eye. Likewise an intravenous injection of isotonic saline solution or the administration of water by means

TABLE 6

GROUP 3C: TESTS WITH PREPARATION 5879
(Aqueous content of potassium and sodium in mE/L.)

Animal Number	Potassium			Sodium		
	Left Eye	Right Eye	Difference	Left Eye	Right Eye	Difference
1	4.17	4.14	0.03	158	142	16
2	4.89	4.78	0.11	167	167	0
3	5.17	4.78	0.39	172	167	5
4	5.47	4.71	0.76	167	162	5
5	4.40	3.84	0.56	167	158	9
$\bar{x}$	4.82	4.45	0.37	166	159	7
$s_{\bar{x}}$			±0.13			±2.66

In Group 3c there is statistically no difference either between the two mean values of the potassium content ($0.10 > P > 0.05$) or between the two mean values of the sodium content ($0.10 > P > 0.05$).

of a gastric tube have no influence on it.

The carbonic anhydrase inhibitors were applied in a high dosage to obtain the maximum inhibition of the carbonic anhydrase activity in the area of iris and ciliary body. According to Ballintine and Maren,[2] dosages of only 10 or 20 mg. Diamox per kg. body weight, given intravenously, are supposed to cause an almost complete inhibition; one might, therefore, expect a maximal effect with the higher dosage administered in our experiments.

Considering the delayed action after oral administration compared to parenteral we left an interval of four hours between puncturing both eyes when using a gastric tube for applying preparations, instead of a three-hour interval with the intravenous administration.

In the second group the action of Diamox and dichlorphenamide were investigated. Diamox caused a significant decrease of the potassium level of 1.28 ± 0.22 mE/L; whereas, dichlorphenamide resulted in a significant lowering of 1.52 ± 0.10 mE/L. The sodium content was reduced by Diamox but not significantly. Dichlorphenamide did not influence the sodium content. From these results one may conclude that, with the dosage given by us. Diamox and dichlorphenamide inhibit to an almost equal extent the carbonic anhydrase activity of the ciliary body.

In the third group Neptazane, Diuril, and preparation 5879 were tested. Neptazane caused a significant lowering of the potassium content of 1.89 ± 0.09 mE/L, Diuril a decrease of 0.56 ± 0.10 mE/L,while the lowering of the potassium level caused by preparation 5879 of 0.37 ± 0.13 mE/L was not significant. The sodium content of the aqueous was reduced insignificantly by Neptazane, Diuril and preparation 5879. According to these results it might be expected that with the dosage given by us, Neptazane would inhibit the carbonic anhydrase activity of the ciliary body in a far higher degree than Diuril and preparation 5879.

According to our present knowledge the inhibition of the carbonic anhydrase activity in the rabbit and in man does not have an identical effect on the composition of the aqueous humor, and therefore the conclusions to be drawn from the experiments described here are conditional.

The present examinations, however, show that the decrease of the potassium content of the rabbit's aqueous caused by the carbonic anhydrase inhibitors used in this series is dissimilar. This is probably the result of an unequally strong inhibition of the carbonic anhydrase activity in the ciliary body in the rabbit eye. Therefore one can expect that in clinical application also, the effect of these drugs upon the intraocular pressure will be dissimilar.

Summary

The influence of various inhibitors of the carbonic anhydrase (Diamox, dichlorphenamide, Neptazane, Diuril and preparation 5879 of the Ciba Company [Esidrex]) on the potassium and sodium content of the aqueous humor of rabbits was examined. It is shown that these drugs cause a decrease of the potassium content, varying in degree, whereas a change of the sodium level could not be proved with certainty.

It is pointed out that the degree of reduction of the potassium concentration in the aqueous humor might be an indicator to the extent of the in vivo inhibition of the carbonic anhydrase activity of the ciliary body.

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REPOSITORY DRUGS IN THE TREATMENT OF TRACHOMA*

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Although sulfonamides and antibiotics have undoubtedly given excellent results in the treatment of trachoma, the manner of their administration and the duration of the treatment make them less suitable for use outside schools and certain communities.

This applies both to areas in which the schools are not attended by all the children of school age, and to "contacts" of patients undergoing regular treatment (for example, children of preschool and postschool age and adults in the families of children under treatment at school). Mass treatment, moreover, requires that the whole population should be treated alike, partly because of the risk of reinfection among children who have been cured by antibiotic or sulfonamide treatment and have left school. This risk, due to the weakness of the immunity conferred by cured trachoma, has been confirmed by Bietti and Ferraris De Gespare[1] in cured patients living in a superendemic environment.

It occurred to us to use "repository" (slowly-absorbed or slowly-eliminated) sub-

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stances in an attempt to solve the problem of giving as full a treatment as possible to communities whose members will not collaborate well and cannot be altogether trusted to treat themselves. They can do so very easily, however, by using antibiotic eyedrops or ointment over a long enough period.

Benzathine penicillin

The first substance we used was a penicillin with a prolonged action, N,N dibenzylethylenediamine dipenicillin G (benzathine penicillin), which has an exceptionally long-continued action and is absorbed gradually. The blood levels are at first low, but therapeutically active concentrations of penicillin are maintained in the serum and tissues for a very long time (fig. 1). This use of penicillin is based on Bietti's[2] observations since 1944 on its effects on the trachoma virus (degeneration and disappearance of inclusions, clinical cure of trachoma). These observations have unfortunately remained unnoticed for a long time. I should like, however, to mention Poleff's[3] and Gilkes' and co-workers'[3b] inclusions studies, and the research of T'ang[4] and his co-workers and of Collier[5] on culture of the trachoma virus, which failed when the sample was treated with penicillin but not with streptomycin. All this work proves beyond doubt that penicillin acts on the trachoma virus.

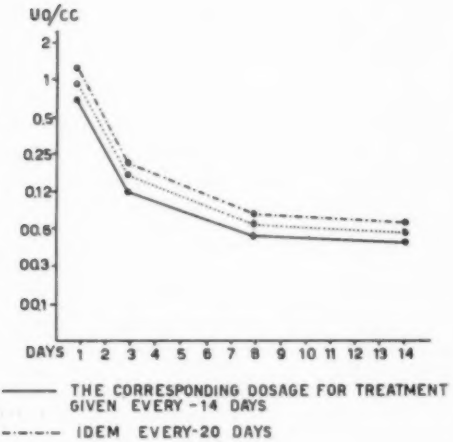


Fig. 1 (Bietti). Concentration of penicillin in blood after injection of 2,500 units/kg. in subjects of 25 to 35 kg. body weight.

My first experiments were performed with my co-worker Pannarale[6] on 35 patients, mostly school children, who all had well-established trachoma.

Eighteen of these patients received an intramuscular injection of DBEP every 14 days, 10 every 20 days, and seven every 30 days. In the first group only eight, in the second only six, and in the third only four injections were given. The treatment therefore took about three months, and the dosage was calculated to give about 2,000 to 2,500 units per kg. of body weight intramuscularly per day. For instance, a child weighing 20 kg. received 900,000 units every two weeks or 1,200,000 every 20 days.

The results obtained four months after the start of treatment were:

a. Of the 18 patients treated every 14 days, 12 were completely cured and two almost completely cured.

b. Of the 10 patients treated every three weeks, seven were completely and two nearly cured.

c. Of the seven patients treated every 30 days, three were completely and two nearly cured.

Two years after the start of treatment the results were even better. Not only had all the patients considered cured four months after the start of treatment remained so, but others had been completely cured. Thus conjunctival hypertrophy had completely disappeared in 16 of the first group of 18 patients (one case was not cured but improved, and another could not be found); nine patients out of the second group of 10 (one case was treated elsewhere by other means), and out of the third group of seven those five patients who could be seen again, were completely cured.

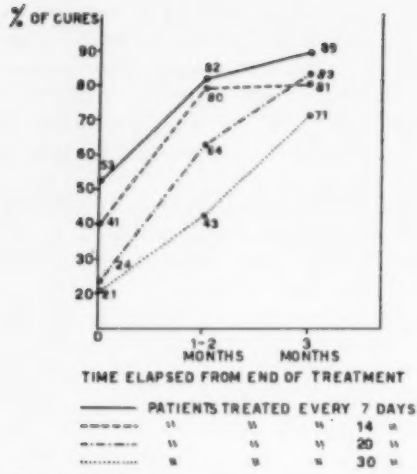


Fig. 2 (Bietti). Percentage of patients cured with benzathine penicillin according to the schedule of administration and the time elapsed from end of treatment.

Inclusion bodies had already disappeared after the first shot of benzathine penicillin.

Benzathine penicillin was used again by my co-worker Pannarale on four groups comprising 198 patients, showing an active trachoma generally of average severity who received the same doses as in the first experiment every seven, 14, 20, and 30 days. After three months' treatment there was complete cure in 53 percent of the cases treated every seven days, in 41 percent of the cases treated every 14 days, in 24 percent of those treated every 20 days, and in 21 percent of those treated every 30 days. Between one and two months after the end of the treatment the residual hypertrophy had resolved and complete cure could be observed in 82 percent of the cases treated every seven days, in 80 percent of the cases treated every 14 days, in 64 percent of those treated every 20 days, and in 43 percent of those treated every 30 days. Between three and five months after the end of treatment there was complete cure in 89 percent of the cases treated every seven days, in 81 percent of those treated every 14 days, in 83 percent of those treated every 20 days, and in 71 percent of the cases treated every 30 days. The most active treatment thus proved to be that given at intervals of seven to 20 days (fig. 2).

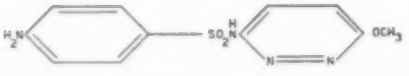
We are also exploring the possibility of treatment by spaced doses of benzathine penicillin per os.

Milano[7] and Brignola[8] and Rende[8b] have also obtained satisfactory results with benzathine penicillin. Yap[9] approves of its use but has not formed a precise opinion concerning its action on the virus, considering its antibacterial action more important.

In spite of these good results, however, benzathine penicillin treatment has the undeniable disadvantages of being costly and of requiring the injection of large doses of suspended antibiotic (especially when the patient has a high body weight). It also causes a certain amount of local discomfort at the site of injection, and sometimes a fever reaction after heavy doses (for example, those given at 30-day intervals). There is also the theoretic possibility of allergy and penicillin anaphylactic shock, though we have never seen them in patients treated with benzathine penicillin. Moreover, if kept in a hot climate, the present preparations of benzathine penicillin G are not absolutely certain to be stable.

Sulfonamides

These considerations induced us to undertake further research, especially since penicillin treatment is certainly useless for the seasonal conjunctivitis of Koch-Weeks associated with trachoma in certain countries. We therefore used a sulfonamide of slow elimination, sulfamethoxypyridazine (Kynex, Cl 13.494, or Lederkyn, fig. 3), kindly put at our disposal by Lederle Laboratories.



(3 SULPHANILAMIDO - 6 - METHOXYPYRIDAZINE)

Fig. 3 (Bietti). Sulfamethoxypyridazine (Kyne orx Cl 13.494 or Lederkyn).

Our first experiments were carried out on 57 patients, mostly children of school age, suffering from trachoma II of average severity.[10] They showed that sulfamethoxypyridazine given in doses of about 8.0 to 12 cg. per kg. of body weight every seven or 10 (sometimes 15) days for three months led to complete cure in 45 cases and to considerable improvement, almost to cure, in the others. These results were noted three months after the end of the treatment; that is to say, spontaneous improvement of incompletely cured cases was still possible. Actually 15 to 18 months after the end of treatment 50 cases were cured and the other seven were improved (table 1). Inclusions usually cannot be found after the second shot of the drug.

I desire to point out that the dosage we used cannot be regarded as final. Good results would quite probably be obtained with still smaller doses.* We believe that for the time being 8.0 to 10 cg. per kg. of body weight every seven to 10 days for three months might be considered an active and practically nontoxic dose. We desire to emphasize that no incident worth noting has resulted from the administration of sulfamethoxypyridazine. Blood counts have shown excellent tolerance, since the only change observed was a certain decrease, between 36.4 and 10 percent, in the number of white cells. This leukopenia is most marked after the two first administrations; it then levels out at an average of 10 to 12 percent. The white cell count returns to normal a few weeks after the end of the

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* Further research still in progress conducted by my co-workers B. Latte and M. Lanzieri on 180 trachomatous individuals (mostly stage II) from Sardinia has actually shown that:

1. The administration of 8.0 cg. of Lederkyn per kg. of body weight every seven to 10 days for three months produced complete or almost complete cure or marked improvement (to be expected to become cured during the next months) in 48 out of 60 patients;

2. The administration of 5.0 cg. of Lederkyn per kg. of body weight every seven to 10 days for three months produced complete or almost complete cure or marked improvement (to be expected to become cured during the next months) in 42 out of 60 patients;

3. The administration of 3.0 cg. of Lederkyn per kg. of body weight every seven to 10 days for three months produced complete or almost complete cure or marked improvement (to be expected to become cure during the next months) in 18 out of 60 patients.

These provisional results await further confirmation at another examination to be done after six months.

The results obtained by another group of my coworkers (P. F. Ferraris De Gaspare and M. Montaldi) among 750 individuals (plus 90 untreated controls) from Tripoli (Libia) affected by trachoma II or III lead to similar conclusions.

Their work (still in progress and awaiting further check-ups) on groups of 30 patients each, has shown so far that:

1. The administration of sulfamethoxypyridazine every seven days for three months was followed, three months after the end of treatment, by (a) 66 percent of cures, when 8.0 cg. per kg. body weight were given; (b) 60 percent of cures, when 5.0 cg. per kg. body weight were given; (c) 30 percent of cures, when 3.0 cg. per kg. body weight were given.

2. The administration of sulfamethoxypiridazine every 10 days for three months was followed, three months after the end of treatment, by (a) 67 percent of cures, when 8.0 cg. per kg. body weight were given; (b) 50 percent of cures, when 5.0 cg. per kg. body weight were given; (c) 24 percent of cures, when 3.0 cg. per kg. body weight were given.

3. The administration of sulfamethoxypyridazine every 12 days for three months was followed, three months after the end of treatment, by (a) 50 percent of cures, when 8.0 cg. per kg. body weight were given; (b) 40 percent of cures, when 5.0 cg. per kg. body weight were given; (C)20 percent of cures, when 3.0 cg. per kg. body weight were given.

By adding aureomycin ointment (one percent, four times a day), the percentage of cures jumped to roughly 70 percent among the patients receiving the lowest dosage of sulfamethoxypyridazine (3.0 cg. every seven to 12 days) and almost to 90 percent among those receiving 8.0 cg.

Aureomycin ointment (one percent) if given alone for three months four times a day, was followed by 60 percent of cures; if given for only four days a month during six months was followed by 30 percent of cures.

The results obtained with sulfamethoxypyridazine correspond very closely to those observed after daily administration of 5.0 cg. per kg. body weight of Gantrisin. When the administration of Gantrisin took place only every seven days, the percentage of cures dropped to 23 percent.

Among the 90 untreated patients only 10 percent improved consistently during the period of observation of six months.

TABLE 1

THERAPY WITH KYNEX FOR THREE MONTHS
(Results obtained 15 to 18 months after the end of the treatment)

	Number of Patients	Recovered	Almost Recovered	Much Improved	Slightly Improved	Unchanged
Group I: 2 gr. every 5 da., 8–9 cg. per kg. body weight	7	7	—	—	—	—
Group II: Sect. A—2 gr. every 7 da., 10–11 cg. per kg. body weight	6	6	—	—	—	—
Group II: Sect. B—3 gr. every 7 da.; 8.1–13 cg. per kg. body weight	10	9	1	—	—	—
Group II: Sect. C—4 gr. every 7 da., 6.4–10.2 cg. per kg. body weight	8	6	2	—	—	—
Group III: Sect. A—2 gr. every 10 da., 9–11.8 cg. per kg. body weight	7	6	1	—	—	—
Group III: Sect. B—2.5 gr. every 10 da., 8.8–11 cg. per kg. body weight	5	4	1	—	—	—
Group III: Sect. C—3 gr. every 10 da., 9–11 cg. per kg. body weight	8	7	1	—	—	—
Group IV: 3 gr. every 15 da., 9–15 cg. per kg. body weight	6	5	1	—	—	—
TOTAL	57	50	7	—	—	—

treatment. Because of this finding we did not feel that we should continue the treatment beyond three months in the more resistant cases, though another course of treatment might perhaps be considered after a two-month rest period.

We also examined our patients' blood sulfonamide level, and noted that a dose of 8.0 to 10 cg. per kg. of body weight of sulfamethoxypyridazine per os gives a maximum concentration of about 17 mg. percent cc. at the 20th hour, and that the figure drops thereafter until on the fifth day it is very low (1.0 to 2.0 mg. percent), which may suggest that the effect on trachoma virus is then very weak (figs. 4 and 5).

A more constant level of the sulfonamides in the blood can, of course, be obtained by giving every day, or every second or third day respectively 0.5, 1.0 and 1.5 gr. of sulfamethoxypyridazine. But these dosages, which have proved in our hands fully effective in trachoma, can only have the aim to reduce the amount of sulfas to be given, while the purpose of using a sulfonamide of slow elimination (given periodically at regular intervals) is to reduce as much as possible the attendance of the patient to the dispensary.

In connection with the inconstant level of sulfas obtained with an intermittent administration of Kynex, we wondered whether the good clinical effects which we have observed could not have been obtained by simply giving ordinary sulfonamide at periodic intervals, and whether it was necessary to maintain any particular concentration in the blood during the succeeding

days. Indeed, during the joint Unicef-WHO campaigns in Morocco and Egypt, Maxwell Lyons[11] and Reinhards[12] noted a beneficial effect on the trachoma when spaced doses of antibiotics (for example, aureomycin ointment twice a day on three or four consecutive days monthly for six or seven months) were applied to the conjunctiva.

To verify this finding we gave two or three gm. (according to weight) of sulfathyazol every seven days for three months to a group of eight children of body weight between 21 and 31.6 kg.

Ten days after the end of the course no change was observed in four, little change in two others, but in the remaining two a well-marked improvement. The reduction of the hypertrophy was not comparable to that obtained in the patients treated with Kynex, but three months after the end of the treatment we noted a later improvement which in two cases proceeded to cure.

Thus, although the administration at periodic intervals of ordinary sulfonamides has a certain effect on the clinical picture of trachoma, this is less marked than the

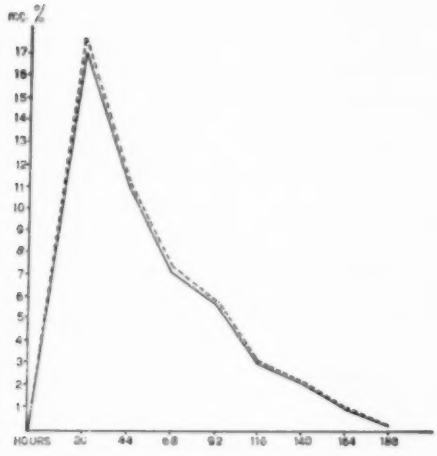

Fig. 4 (Bietti). Concentration of sulfonamide in blood after administration of 8.0 cg. of sulfamethoxypyridazine/kg. body weight. Solid line: free sulfonamide. Broken line: total.

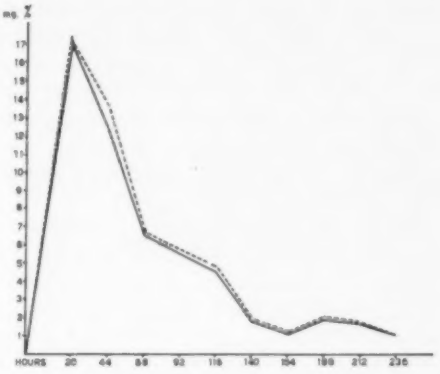

Fig. 5 (Bietti). Concentration of sulfonamide in blood after administration of 10 cg. of sulfamethoxypyridazine/kg. body weight. Solid line: free sulfonamide. Broken line: total.

effect of the same dose of a slowly-eliminated sulfonamide which maintains after five to seven days' administration a bacteriostatic concentration in the blood and tissues which, even though minimal, persists much longer than that produced by ordinary sulfonamides.

If it could be confirmed that the local intermittent antibiotic treatment (Maxwell Lyons-Reinhards) is equally effective in trachoma without bacterial contamination, the conclusion could be drawn that, since the same results cannot be obtained with spaced doses of ordinary sulfonamides, therefore antibiotics and Kynex act on the trachoma in a slightly different way: the antibiotics are active even if the action is limited to three days a month, but the sulfonamides must be present in the blood for longer in order to be fully active.

We may have to do more research in order to arrive at a dosage which will be more suitable, economical, practical, effective, and of minimal toxicity, and in order to study the influence of sulfonamide therapy with Kynex on the pathogenic bacterial flora associated with the trachoma (chiefly the Koch-Weeks bacillus). Nevertheless, it seems possible to state at present that slowly eliminated sulfonamides promise to be very

useful in the mass treatment of trachoma especially in antibiotic-resistant cases (10 to 30 percent according to Reinhards). This has been recently confirmed by Rochat.[13]

They may sometimes be combined with local intermittent antibiotic treatment, especially in regions where associated bacterial conjunctivitis is a major problem.

Other slowly eliminated sulfonamides (mainly sulfaphenazol) are now being tested. It may be that they will be as effective as sulfamethoxypyridazine has been shown to be.

Summary

The results of the clinical use in trachoma of "repository drugs" (slowly absorbed or eliminated substances: benzathine penicillin and sulfamethoxypyridazine) are reported.

The administration of benzathine penicillin as intramuscular injections for three months every seven to 14 to 20 days (2,500 to 2,000 units per kg. body weight per day) resulted in clinical cure of over 80 percent of patients (89 percent every seven days).

Also the administration of sulfamethoxypyridazine at the dosage of 8.0 to 10 cg./kg. body weight every seven to 10 days for three months proved equally effective.

The results have to be checked at about six months after the end of treatment, since a spontaneous improvement takes place after cessation of therapy.

This intermittent schedule of treatment, especially with sulfamethoxypyridazine, which, from the practical point of view, has several advantages over penicillin, is particularly to be recommended for mass treatment to communities whose members will not or cannot collaborate with the ordinary way of treatment with antibiotics. Sulfamethoxypyridazine, moreover, offers the advantage of reducing the dosage in the ordinary therapy schedule of trachoma, as well as of other ophthalmic infectious diseases. It may also be used with benzathine penicillin and local antibiotics in special cases.

University of Rome.

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CORRECTION OF UP-DRAWN OR "TEAR-DROP" PUPIL

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The condition to be discussed in this paper is an up-drawn or "tear-drop" shaped pupil (fig. 1) seen the next day following an uncomplicated intracapsular cataract extraction and also late occurrence seen as long as several months after the operation.

This disturbing complication is due either to the iris or a strand of the zonule or vitreous being pinched in the wound. It is thought to be caused by:

1. An incomplete clearing of the wound before closing at the time of operation.
2. Faulty apposition of the lips of the wound.
3. Gaping of the posterior lip of the wound caused by a tight suture.
4. Squeezing after the akinesia of the orbicularis has worn off.
5. Trauma.

The tendency is not to try to correct the "tear-drop" pupil and occasionally the end-result is good with 20/20 vision or better, but this is the exception. In the area of the cornea corresponding to the eccentric pupil, the astigmatism is usually greater so that the vision is reduced as much as two or three lines on the Snellen chart with the usual aphakic correction. Possibly the vision might be improved with a contact lens, but I have not tried using one when this complication has been present.

Until last year the only treatment that I have used to try to correct the "tear-drop" pupil when seen early was to instill a miotic and allow one-half to one hour to produce more miosis.* Then after anesthetizing the eye, pressure was exerted with the end of a glass rod or spatula on the wound at the site where the iris appeared to be adherent. In only one instance was the iris freed by this procedure and a round pupil restored.

Fortunately the "tear-drop" pupil is not a common occurrence and, until last year, considerable time had elapsed without my seeing one. I thought that greater care used in clearing and closing the wound had eliminated this complication. Then one morning about a year ago a "tear-drop" pupil was present at the first dressing and a week later two more occurred all on the first day following uneventful intracapsular extractions. The anterior chambers were of normal aphakic depth. When the first of the three was observed it was decided to try to free the iris directly by means of a spatula introduced into the anterior chamber. It was the right eye and the adhesion appeared to be at about the 11-o'clock position.

PROCEDURE

The same preanesthetic medication was used as for the cataract extraction: pentobarbitol sodium (Nembutal) (0.1 gm.), meperidine hydrochloride (Demerol) (75 mg.), Phenergan hydrochloride (12.5 mg.). An hour and a half were allowed for the

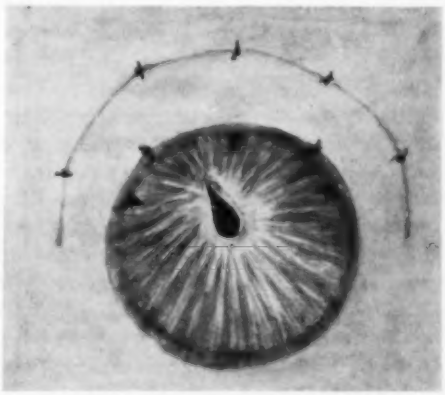

Fig. 1 (Atkinson). "Tear-drop" pupil.

* Following operation and before applying the dressing pilocarpine (two percent) and eserine (0.25 percent) are usually instilled in the eye after a round pupil extraction has been done.

medication to take effect before the patient was taken to the operating room. Akinesia of the orbicularis was obtained by block of the facial nerve. Tetracaine (Pontocaine) hydrochloride (0.5 percent), epinephrine (1:1000), and pilocarpine (two percent) were instilled. An injection of lidocaine hydrochloride (Xyclocaine) (two percent) with hyaluronidase (Wydase) was given under the conjunctiva and Tenon's capsule in the sector corresponding to the up-drawn pupil. A few minutes were allowed for this to take effect.

A spatula was introduced under the conjunctival flap at about the 10-o'clock position then into the anterior chamber angle, temporal to the point of the "tear-drop" pupil. The spatula was then swept down, pressing back on the iris as is sometimes done at the time of operation to replace the iris. The pupil immediately became round and central and the spatula was withdrawn with very little loss of aqueous. Pilocarpine (two percent), eserine (0.25 percent) and Neosporin were then instilled and a monocular dressing applied.

The same procedure was used with the other two patients. The recovery in all three was uneventful.

In these cases the "tear-drop" pupil was thought to be due to an adhesion of the iris to the wound or to a strand of the zonule, since slitlamp examinations about three weeks later showed the hyaloid to be intact.

Fortunately no "tear-drop" or up-drawn pupils have been observed early in the postoperative course since the three just reported. However, two patients whose pupils were round and central when seen two months after the operation had "tear-drop" pupils when seen again several months later. In these cases the eyes were quiet and the vision was reduced in one instance from 20/20 to 20/40 and in the other from 20/15 to 20/100. Probably a "corepraxy" as advocated by Franceschetti[1] or an iridectomy as reported by Chandler[2] could be used to improve the vision in these eyes.

The late occurrence of the "tear-drop" pupil, an indication that the wound has been opened, clinically confirms the observation of Henderson[3] in 1907, that two or more months are required for the firm healing of the cataract incision. More recently this has been confirmed by Maggiore[4] and Dunnington.[5] Dunnington in his Bowman Lecture called attention to the investigation of Gliedman and Karlson[6] who found the tensile strength of limbal incisions in cats was only 62 percent of normal tissue six months after operation.

With this convincing evidence in regard to the length of time required for firm healing of the cataract incision it would seem advisable to caution our patients in regard to squeezing, rubbing the eye, and other trauma for at least three or four months after the operation, possibly longer.

Summary

The occurrence of a "tear-drop" pupil is not a frequent complication but may affect the vision considerably. It may be seen early or not until two months or more after the operation. The principal causes are improper wound closure, squeezing, or trauma.

Direct freeing of the iris with a spatula proved successful in three eyes in which it was present at the first dressing. The occurrence of this complication is an added stimulus to inspect and clear the wound more carefully at the completion of the extraction and to strive for an accurate apposition of the lips of the wound and a firm closure.

Careful attention to postoperative sedation in nervous, apprehensive patients may help prevent this complication. Patients should be warned to guard against squeezing, pressure on the eye, or trauma for at least three or four months after a cataract extraction.

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HISTOCHEMICAL STUDIES ON THE NORMAL AND SWOLLEN CORNEA

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Recently, while investigating the reactions of the cornea to a variety of stains in common use for the demonstration of acid mucopolysaccharide, it was found that the normal cornea behaved quite differently from the tissue in its swollen state. The staining methods employed were (1) metachromasia to toluidine blue (Lillie), (2) Alcian blue 8 GS (Steedman), (3) dialyzed iron method of Hale (Rinehart-Abul-Haj modification), and (4) the periodic-acid-Schiff reaction (PAS).

The anterior segments of the left and right eye of a rabbit were removed at death, one segment being placed immediately into 10-percent formol saline and the other segment being left in distilled water for 12 hours to allow maximum swelling to occur in the cornea before transferring to fixative.* Paraffin sections, mounted at 37°C., were then stained by the four methods and the distribution and intensity of the stain were compared in the two corneas.

*In this work it was found that four-percent basic lead acetate had no important advantage over formol saline; while Carnoy's fluid, which has been recommended to avoid loss of water-soluble mucopolysaccharides, gave entirely unsatisfactory results.

1. Metachromasia

Metachromasia is a highly complex phenomenon and the results obtained in tissues vary considerably according to the fixative employed, the concentration and pH of the dye solution used, and the use of alcohol in preparation, since both alcohol-sensitive and alcohol-resistant forms of metachromasia occur. With the method used in the present study, namely that of Lillie (1954), which utilizes 0.5-percent toluidine blue at pH 4.0, the results obtained correspond exactly to those of Wislocki (1952) who found metachromasia in the corneal stroma and Bowman's membrane, whereas Descemet's membrane reacted orthochromatically.

Our sections also showed that the beta metachromasia of the stroma was uniform and extended further along the inner side of the cornea than the outer side, but did not reach the trabecular region.

Comparison of metachromasia of the *normal* cornea with the *swollen* cornea showed a diminution of intensity from ++++ to ++ and a change from beta metachromasia (violet) to gamma metachromasia (red) (figs. 1 and 2; table 1).

TABLE 1

COMPARISON OF INTENSITY OF VARIOUS STAINING REACTIONS IN THE NORMAL AND SWOLLEN CORNEA OF THE RABBIT

Stain	Normal	Swollen
Toluidine blue (metachromasia)	++++ (violet)	++ (red)
Alcian blue *without* counter-stain	++ (light blue)	++++ (dark blue)
Alcian blue *with* counter-stain	+ (light blue) Heavy counter-staining	++++ (dark blue) Faint counter-staining
Rinehart *without* counter-stain	++ (light blue)	++++ (dark blue)
Rinehart *with* counter-stain	++(blue posteriorly) Heavy counter-staining	++++ (dark blue) Faint counter-staining
PAS	+++ (red)	++ (pink)
Eosin	++++	++
Light green	++++	++

2. ALCIAN BLUE

Lison's (1954) modification of Steedman's (1950) Alcian blue method for acid mucopolysaccharides was used both with and without the counter-stain of chlorantine fast red.

Without counter-stain the normal cornea showed a fairly uniform light blue (++) staining with a slight tendency to a posterior concentration, while the *swollen* cornea showed an intense dark blue (++++) with a similar distribution (figs. 3 and 4).

With counter-stain the two preparations showed an even greater contrast of blue (from + to ++++) since the collagen fibers, which normally stain with chlorantine fast red, apparently lost this property in the swollen cornea (figs. 5 and 6; table 1).

3. DIALYZED IRON METHOD OF HALE (RINEHART-ABUL-HAJ MODIFICATION)

This method is based on the affinity of acid mucopolysaccharides for colloidal iron, which are subsequently rendered blue with potassium ferrocyanide (Prussian blue reaction). The modification described by Rinehart and Abul-Haj (1951) was thought by them to demonstrate acid mucopolysaccharide more readily than the technique of Hale, but the stain is not specific for acid

»»→

Figs. 1-12 (Ashton). Histochemical studies on the normal and swollen cornea.

Fig. 1. Normal rabbit cornea showing intense beta metachromasia in the stroma extending further along the inner side than the outer.
Fig. 2. Swollen cornea of rabbit, showing marked loss of metachromasia. Compare with Figure 1.
Fig. 3. Normal rabbit cornea stained with Alcian blue and no counter-stain.
Fig. 4. Swollen cornea of rabbit stained with Alcian blue. Shows marked increase in intensity of staining. Compare with Figure 3.
Fig. 5. Normal rabbit cornea stained with Alcian blue and chlorantine fast red. The blue staining is largely obscured by the counter-staining of the collagen.
Fig. 6. Swollen cornea of rabbit, stained with Alcian blue and chlorantine fast red. The cornea now stains an intense blue due partly to an increased uptake of Alcian blue and partly to loss of collagen staining (as can be seen at the limbus). Compare with Figure 5.
Fig. 7. Rabbit cornea, normal (above) and swollen (below), stained with dialyzed iron. No counter-stain has been used. In the normal cornea staining is most marked posteriorly whereas in the swollen cornea it is uniform and much more intense.
Fig. 8. Normal rabbit cornea stained with Rinehart-Abul-Haj technique. The counter-stain of cochineal obscures the blue staining.
Fig. 9. Swollen cornea of rabbit. The cornea now stains an intense blue, due partly to a greater uptake of iron and partly to loss of collagen staining. Compare with Figure 8.
Fig. 10. Normal rabbit cornea stained with PAS. Note the distribution of red staining which is particularly intense in Descemet's membrane.
Fig. 11. Swollen cornea of rabbit, showing great diminution of the PAS reaction, which is, however, retained in Descemet's membrane. Compare with Figure 10.
Fig. 12. Cornea of rabbit, normal (above) and swollen (below), stained with light green. Note the fainter reaction of the swollen cornea.

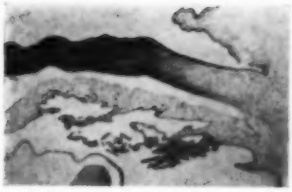

Fig. 1

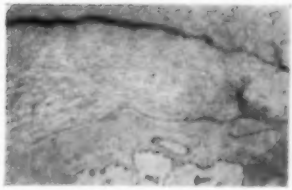

Fig. 2

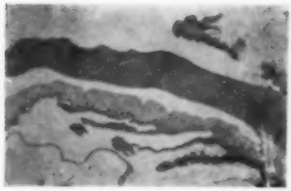

Fig. 3

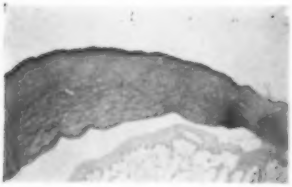

Fig. 4

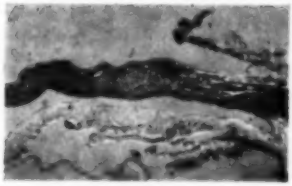

Fig. 5

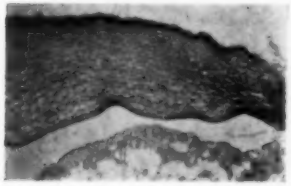

Fig. 6

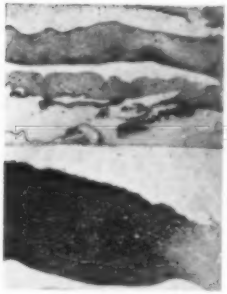

Fig. 7

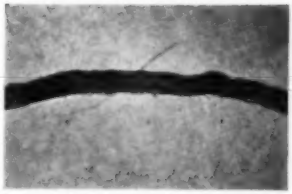

Fig. 8

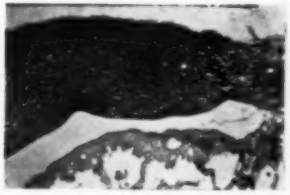

Fig. 9

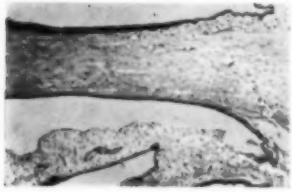

Fig. 10

Fig. 11

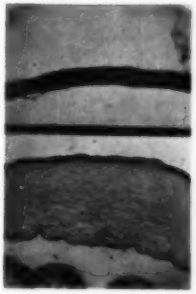

Fig. 12

mucopolysaccharides and provides only suggestive evidence of their presence. In the present study the method was used with and without the counter-stain of cochineal.

Without counter-stain the *normal* cornea stained a pale blue (++) which at the periphery was more marked posteriorly, while the *swollen* cornea showed an intense blue (++++) which was uniformly distributed (fig. 7).

With counter-stain the *normal* cornea stained red anteriorly and blue (++) posteriorly; some preparations showed no central blue staining. It was evident that the red staining of the collagen masked the blue of the corneal mucoid, which was most blue where the collagen was least dense, that is, posteriorly and peripherally. In the *swollen* cornea there was an intense blue staining (++++) with uniform distribution, and the cornea completely failed to take up the counter-stain (figs. 8 and 9; table 1).

4. Periodic acid-Schiff stain

By this method mucopolysaccharides are oxidized to polyaldehydes by periodic acid and the preparation is then stained with fuchsin-sulfite (Schiff's reagent). The significance of a positive reaction (red-staining) is as yet undecided, but it is certainly not specific for mucopolysaccharides, for in addition to reacting with other polysaccharides it also gives positive results with mucoproteins, glycoproteins, glycolipids, and unsaturated lipids and phospholipids (Pearce, 1953). As regards the cornea, our observations are in accord with those of Wislocki (1952) who found a PAS-positive reaction in the anterior corneal epithelium, in the epithelial basement membrane, in the substantia propria, and in Descemet's membrane.

In the present study, in which the original technique of Hotchkiss (1948) was used, the *normal* cornea showed a strong red staining (+++) of the stroma, somewhat more marked anteriorly. Descemet's membrane was more intensely stained (++++). In the *swollen* cornea the stromal staining was less marked showing a pink (++) compared to the normal red. Descemet's membrane was unchanged (figs. 10 and 11; table 1).

Summary of findings

The *normal* rabbit cornea shows beta metachromasia with toluidine blue, and stains positively with Alcian blue, with dialyzed iron, and with PAS. The dialyzed iron and Alcian blue tend to stain more positively in the posterior cornea; the reverse is true with PAS.

In the *swollen* cornea the intensity of the blue stain given by Alcian blue or dialyzed iron is increased to a remarkable degree, and the cornea fails to take up the counterstain. With PAS and toluidine blue, however, the reverse occurs, both the intensity of red (PAS) and metachromasia (which changes from violet to red) being greatly reduced in the swollen tissue. Simple stains for collagen, such as eosin and light green (fig. 12), also give a fainter reaction in swollen corneas.

Discussion

Changes in the degree of metachromasia as between the normal and abnormal cornea have previously been reported by Gemolotto (1955), who noted that experimental keratitis in rabbits resulted in a decrease in metachromasia when the cornea became opaque, and by de Vincentius (1956) who found an increase in corneal metachromasia in rabbits after severing the ciliary nerves and vessels. In a study of stored corneas Günther (1953) showed that metachromasia gradually diminished with the duration of storage, and after 30 days could no longer be demonstrated. Similarly Nemetz (1958) found that the stored cornea gradually lost its basophilic reaction to methylene blue and this was accompanied by a significant decrease in its swelling capacity. The literature apparently contains no further reference to the effect of corneal swelling on metachromasia and no reports have been

found of the influence of swelling on the uptake of Alcian blue or dialyzed iron, although Grant and Kern (1956) have studied the converse question of the influence of metals on corneal swelling.

As already emphasized the staining methods used in this investigation are not entirely specific for acid mucopolysaccharides, nor is it known which particular mucopolysaccharide or group of mucopolysaccharides a positive result might identify. It is known, however, that these staining properties vary between mucopolysaccharides; for instance substances exhibiting iron-affinity or the aldehyde reaction are not necessarily metachromatic, so that the staining reactions of normal and swollen corneas may well reflect the behavior of different components.

Diminution in intensity of staining of the swollen cornea, as occurs with toluidine blue, PAS, and collagen stains, may be due to a variety of changes coincident with the uptake of water, such as alteration of the pH of the tissue, or depolymerization, dilution, or even removal of the reacting fraction, and, in the case of collagen, to a reduction in the density of the fibers or to some alteration in their ultramicroscopic structure.

The increase of intensity of staining, as occurs with Alcian blue and iron, may possibly be due to the provision of more available reacting groups as a result of depolymerization of the corneal mucoid.

The difficulties in interpreting these histochemical reactions, however, are at the moment too great, and further information is required before these observations on the swollen cornea can be fully understood. Meanwhile they provide a histologic method for recognizing corneal swelling and give a rough indication of the degree of corneal hydration; they further suggest that histochemical studies on the cornea should in future be evaluated more cautiously, for clearly difference in the intensity of staining with these techniques does not necessarily imply a variation in quantity, but possibly only a change in the physical or chemical state of the collagen-mucoid complex.

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